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HAEMORRHAGIC BRIGHT'S DISEASE

II. Prognosis, Etiology and Treatment[1]

THOMAS ADDIS

From the Department of Medicine, Stanford University Medical School, San Francisco

Yesterday the disease was treated as though it had an independent existence. By the device of dealing only with averaged results from groups of patients an attempt was made to eliminate the variations which arise from the fact that the disease, as it actually exists in any given individual, is modified by his particular constitution, by his past history and by the other diseases with which he may be afflicted. The abstract and generalised view obtained by this method of averages has its uses. But in relation to prognosis in the individual patient its use is indirect. A general rule makes it possible to recognise exceptions. Since each patient is in himself unique, every instance of the disease is an exception, and the average serves only as a base-line in the evaluation of the effect of those factors which yesterday we tried to eliminate. But the capacity to predict the fate of individual patients for any but the immediate future does not rest on any organised experience. The study of the influence of constitutional peculiarities and of the deflections produced by other diseases has scarcely begun. Such observations as exist are too scattered and too much influenced by special conditions to provide any real help. This matter lies still in the field of clinical intuition. It is a question for the subconscious summing of vaguely apprehended indications. What is intended here by the term prognosis is something much less complex. It is the extrapolation of curves which depict the extent of the renal lesion.

Sediment counts are often essential for diagnosis. In prognosis they give information in regard to changes in the activity of the lesion, and allow us to follow, rather than to predict, the gradual evolution

[1] Delivered before the Johns Hopkins Medical Society as his Second Thayer Lecture in Clinical Medicine, on May 12, 1931.

of the lesion as it moves from stage to stage. At times such information is decisive. The sediment from the dilute urine of the terminal stage in which only broad renal failure casts are found has an unequivocal significance. But a general knowledge as to the drift of change in the activity or intensity of the lesion is not enough in a disease in which death comes so often as a result of a slow dissolution of the renal architecture by processes which leave the urinary sediment unaffected. In any two patients the intensity of the lesion might be equal, and yet one might be well on the way to complete recovery while the other might be drawing near to death in uremia. To distinguish between them a knowledge of the direction of change in the extent of the lesion is required.

The extent of a renal lesion is measured by determining the amount of tissue which is still functioning. This is an anatomical quantity, as anatomical as casts or cells. The means whereby it is obtained are physiological, but the conditions observed are designed to eliminate all the fluctuations in function in response to changes in the environment which are the special objects of interest for physiology. It is when a measured variable in the environment of the kidney (in this case the concentration of urea in the blood) is given an all-predominant influence, and when conditions require the full activity of all the renal elements that function (in this case the rate of urea excretion), becomes, when judged in relation to the environment, a measure of the structure by means of which it has been accomplished.

Individual instances of changes in the extent of the lesion are given in figures 1 to 9, along with concomitant measurements of its intensity.[2] A glance at the curves in circles which represent the changes in the percentage of kidney tissue still functioning shows that it is not only possible to know whether the amount of functioning tissue is increasing, decreasing or remaining constant, but that over years there is sufficient constancy to give some basis for predictions as to the rate of change, and so obtain at least one important objective element required in prognosis.

[2] In order to reduce the rates of cast, red blood cell, white blood cell, epithelial cell and protein to one quantity which may be regarded as an expression of the intensity of the lesion, the deviations above the upper limits of normal variation have been averaged. In the absence of any real knowledge as to the relative significance of these various rates with respect to intensity, this method may be

Apart from their interest in relation to individual patients these changes in the extent of the lesion raise questions which have a general clinical and pathological significance, though here nothing can be said which is not of the nature of surmise and speculation. Figure 1 shows an instance, not uncommon, of a rapid increase in the amount of functioning tissue. Within a few months after the commencement of the lesion the quantity increases from almost zero to 100 per cent. What is the mechanism behind this restitution? It suggests that glomerulitis is not always an irreversible lesion, that many swollen, occluded glomeruli, for a time almost functionless, may again become active. Quantitative counts of the number of glomeruli in the kidneys of patients who are known to have manifested this form of rapid restitution would provide evidence on this question.

Figures 2 and 3 are examples of a slower and less complete restitution from the depression of the initial stage, while figure 4 shows the course in a patient in whom the amount of renal tissue did at last approach the normal value. But it will be observed that the time scale is not in months but in years. It is remarkable that this gradual rebuilding of the structure of the kidney should occur in the presence of a still continuing lesion. It is the more astonishing when it is

---

used for the sake of convenience, though it cannot be justified on any other ground. An example will make the manipulation clear.

	UPPER LIMIT OF NORMAL VARIATION—RATES PER 12 HOURS	ACTUAL RATES PER 12 HOURS	NUMBER OF TIMES BY WHICH THE ACTUAL RATE EXCEEDS THE UPPER LIMIT OF NORMAL VARIATION
Casts	5,000	50,000	10
Red blood cells	1,000,000	100,000,000	100
White and epithelial cells	1,000,000	8,000,000	8
Protein	100	1,000	10
Total			128 (average = 32)

The average deviation, 32, is plotted as a measure of the intensity or activity of the lesion.

The same ordinate scale is used both for the intensity and for the extent of the lesion. But the scale reads in percentage values as regards changes in extent. The figure 100 represents 100 per cent of the usual amount of kidney tissue.

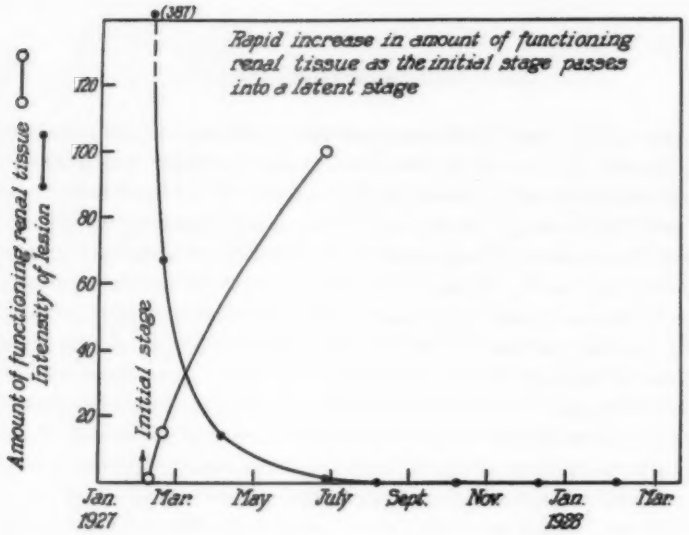
(387)
Rapid increase in amount of functioning renal tissue as the initial stage passes into a latent stage
Amount of functioning renal tissue
Intensity of lesion
120
100
80
60
40
20
Initial stage
Jan. 1927
Mar.
May
July
Sept.
Nov.
Jan. 1928
Mar.

FIG. 1

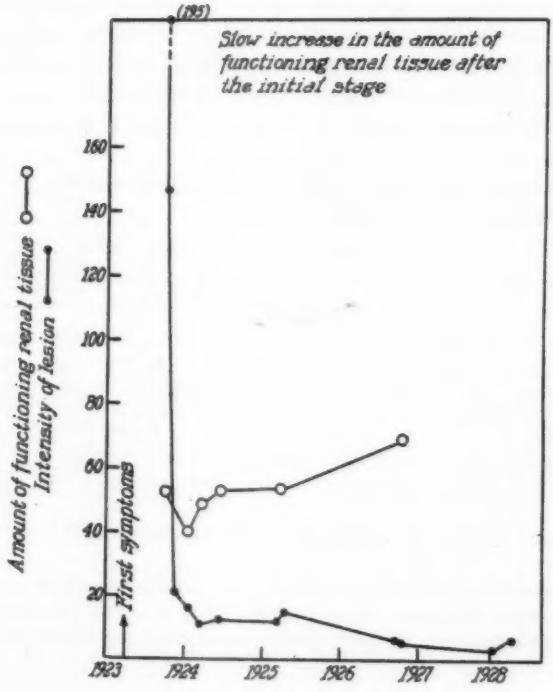
(185)
Slow increase in the amount of functioning renal tissue after the initial stage
Amount of functioning renal tissue
Intensity of lesion
160
140
120
100
80
60
40
20
First symptoms
1923
1924
1925
1926
1927
1928

FIG. 2

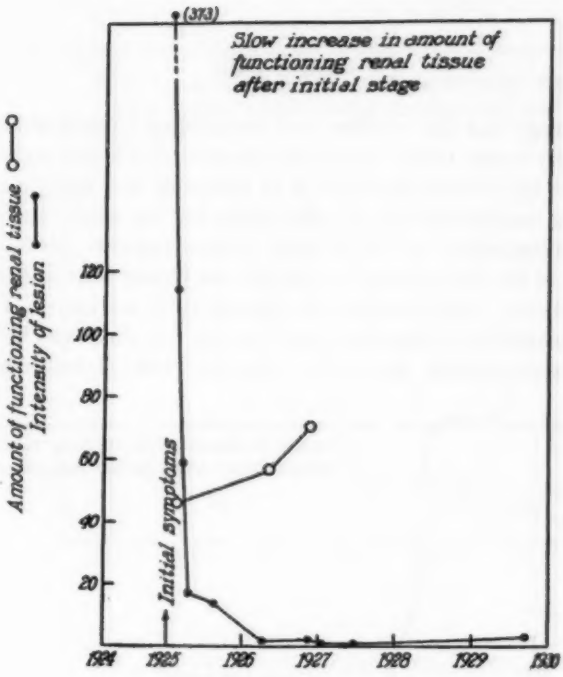
(373)
Slow increase in amount of functioning renal tissue after initial stage
Amount of functioning renal tissue
Intensity of lesion
120
100
80
60
40
20
Initial symptoms
1924
1925
1926
1927
1928
1929
1930

FIG. 3

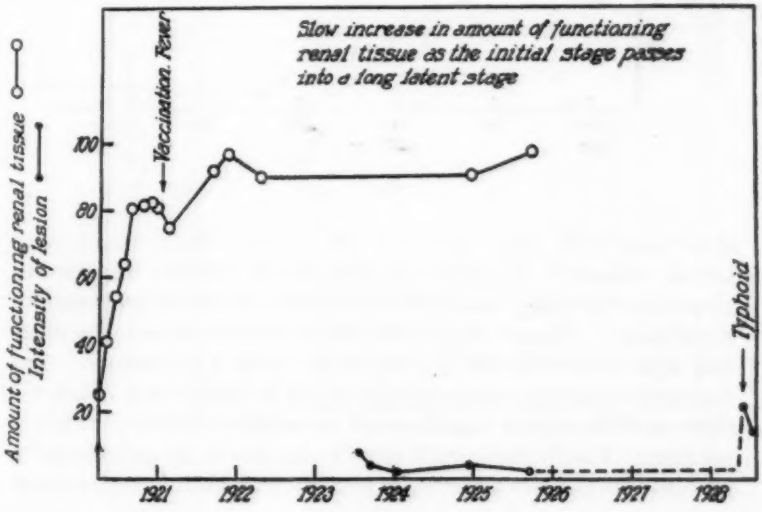
Slow increase in amount of functioning renal tissue as the initial stage passes into a long latent stage
Amount of functioning renal tissue
Intensity of lesion
Vaccination Fever
Typhoid
100
80
60
40
20
1921
1922
1923
1924
1925
1926
1927
1928

FIG. 4

remembered that the constant and outstanding lesion is glomerulitis. Even very severe tubule lesions may be perfectly healed by regeneration, but there is no regeneration of glomeruli, and beyond a certain degree of damage not only the glomerulus but the whole renal element forever disappears. In the kidneys of these patients can be seen the remains of the destroyed glomeruli and the fibrous strands which once were tubules. Nevertheless, the clinical facts are clear. They call for an anatomical explanation, and the only one which can be found is the long-established and often reiterated but clinically neglected

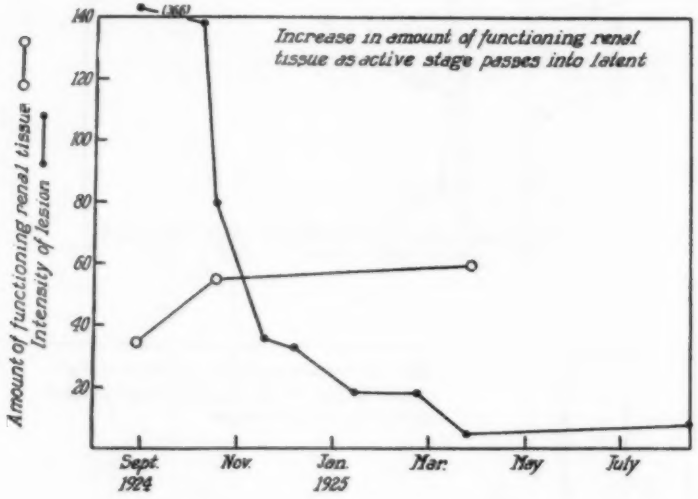

FIG. 5

observation that those glomeruli and tubules which remain have become enlarged. Prognosis depends on the balance between the glomeruli-destroying lesion and the reparative process of compensatory hypertrophy. Figure 5 shows that some restoration of secreting tissue may occur even while the activity of the lesion is pronounced. But the next two patients whose course is shown in figures 6 and 7 show the more usual decrease of renal tissue as the active passes into the terminal stage. Finally, in figures 8 and 9 we see how in the end reparative processes fail and how patients, for so many years entirely well, come at

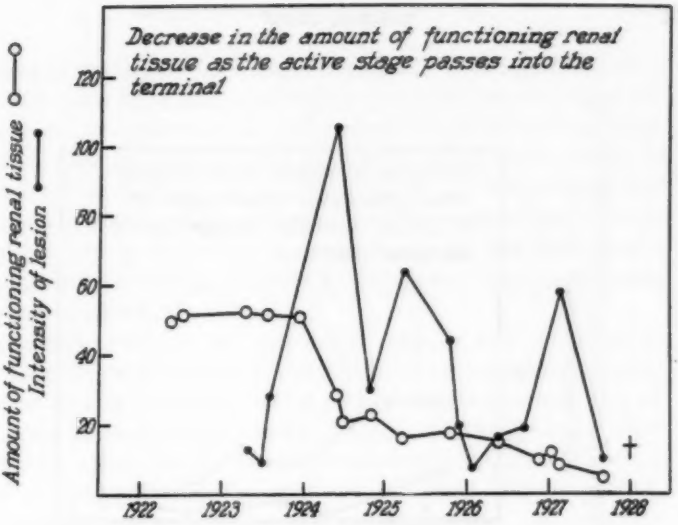
Decrease in the amount of functioning renal tissue as the active stage passes into the terminal
Amount of functioning renal tissue
Intensity of lesion
120
100
80
60
40
20
1922
1923
1924
1925
1926
1927
1928
†

FIG. 6

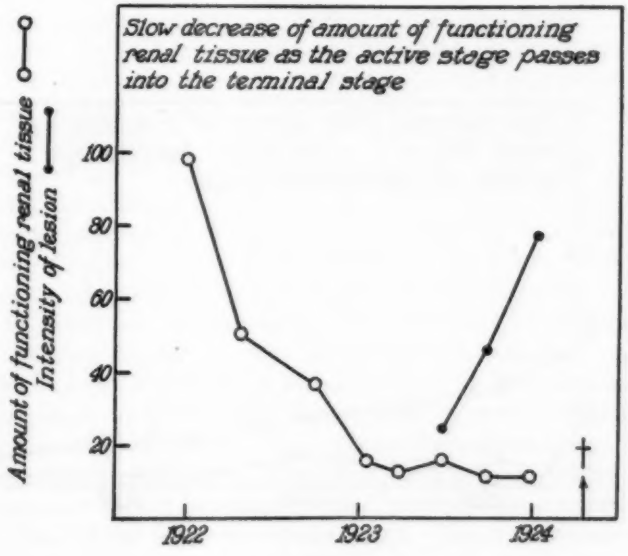
Slow decrease of amount of functioning renal tissue as the active stage passes into the terminal stage
Amount of functioning renal tissue
Intensity of lesion
100
80
60
40
20
1922
1923
1924
†

FIG. 7

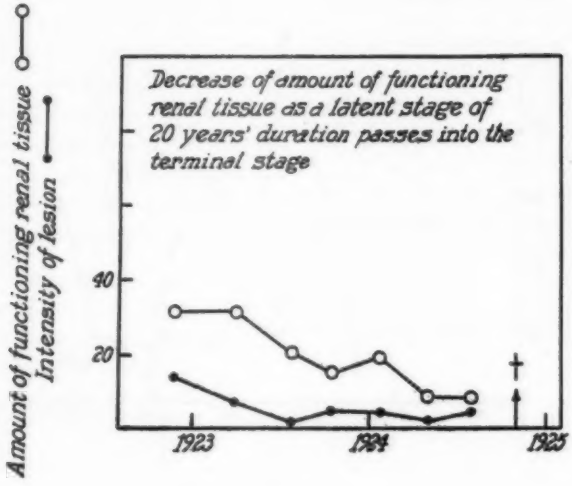
Amount of functioning renal tissue
Intensity of lesion
Decrease of amount of functioning renal tissue as a latent stage of 20 years' duration passes into the terminal stage
40
20
1923
1924
1925
†

FIG. 8

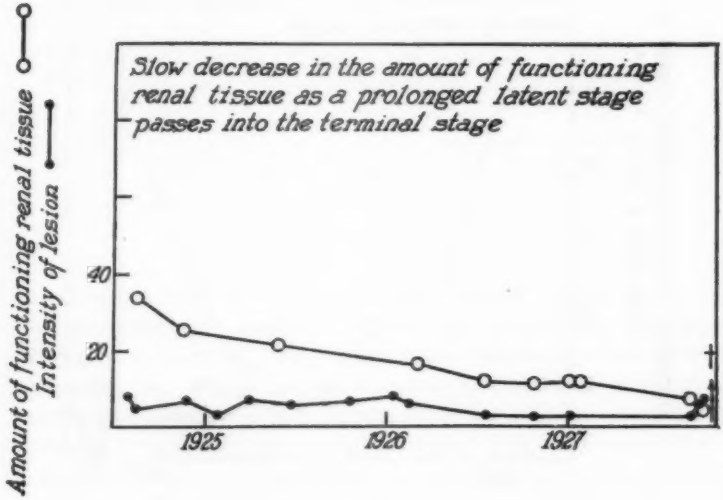
Amount of functioning renal tissue
Intensity of lesion
Slow decrease in the amount of functioning renal tissue as a prolonged latent stage passes into the terminal stage
40
20
1925
1926
1927
†

FIG. 9

last to drift slowly towards death in uremia. It is significant that, in all such cases in which a post-mortem examination was made, Dr. Oliver found an arteriosclerosis and endarteritis of the renal arteries, so that it may be that the final decrease in renal tissue should be ascribed not to a direct failure of compensatory hypertrophy but rather to a limitation of the process imposed by unfavorable nutritive conditions. For it should be noted that he did not find this vascular disease in patients who died earlier in the disease from causes other than renal insufficiency.

Hypotheses, more or less reasonable, may be thus advanced to account for the varying states of equilibrium observed to exist between the lesion and the processes which make towards recovery, but all these leave untouched the central mystery of the disease. How does it come about that for years and decades an apparently healthy individual can harbor a pathological process which, in part at least, is "acute" since it results in a constant haematuria, desquamation of renal cells and proteinuria? There are no analogies by which the question can be analysed, for in no experimental glomerulitis has this most characteristic peculiarity of the disease been reproduced.

At present the most favoured supposition is that the long continuance of the lesion may be due to the more or less constant influx to the kidney through the blood stream of some toxic material formed in a focus of infection elsewhere in the body. But the removal of tonsils and teeth and the draining of infected sinuses does not seem to have any permanent effect on the disease. Any operation may be followed by a transient increase in the intensity of the lesion but later there is no lasting decrease. So far as the clinical evidence goes, it is in favour of the view that not focal but only general toxic states have any measurable effect and even these only while they last. Examples are given in figures 10 and 11. The various incidents and infections which led to temporary increases in the intensity of the lesion were all accompanied by general disturbances such as fever. But none even of these obvious illnesses seem to have been followed by any permanent increase in activity, nor do they seem to have resulted in any irreparable loss of secreting tissue. However, these negative clinical observations have no decisive value. The implications of the many possible modifications of this theory can be developed and

tested only by such special bacteriological and immunological methods as are now being employed in this school by Dr. Longcope and his collaborators.

But it is possible to formulate another and a therapeutically less hopeful hypothesis to account for the long maintenance of an active and progressive lesion in the absence of any obvious cause. Many

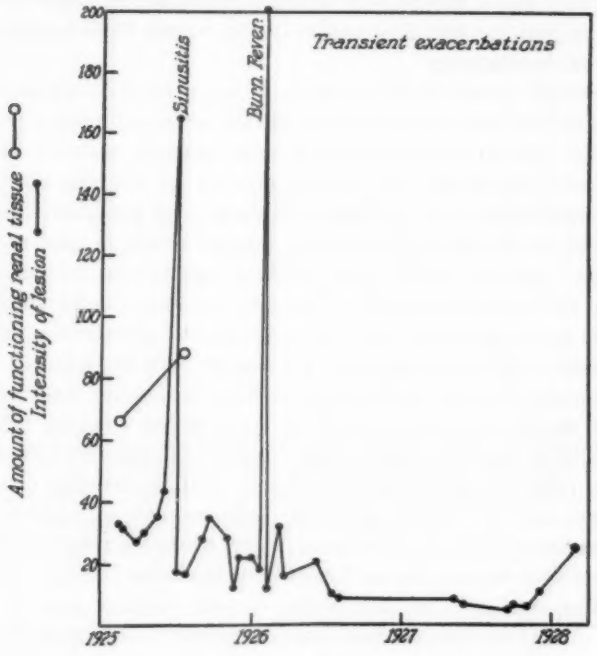

FIG. 10

years ago E. C. Dickson observed that rabbits and guinea-pigs given one injection of a uranium salt showed a still continuing inflammatory reaction in their scarred and contracted kidneys when they were killed long after they had received that single dose. We know that the kidneys he examined were not those which had originally been damaged, for every cell had been many times renewed. We know that no minutest trace of uranium can have been left anywhere within

the body. And yet the pathological process was still continuing in the absence of the agent by which it had been initiated and in a medium which had never known uranium. So also in Haemorrhagic Bright's disease it is possible to suppose that the continuance over years and decades of a slow disintegration of the architecture of the kidney might be a result of the structural disorganization produced in the initial stage of the disease. It would not then be necessary to hypothecate the continuing action of any toxin. The scarlatinal endotoxin might

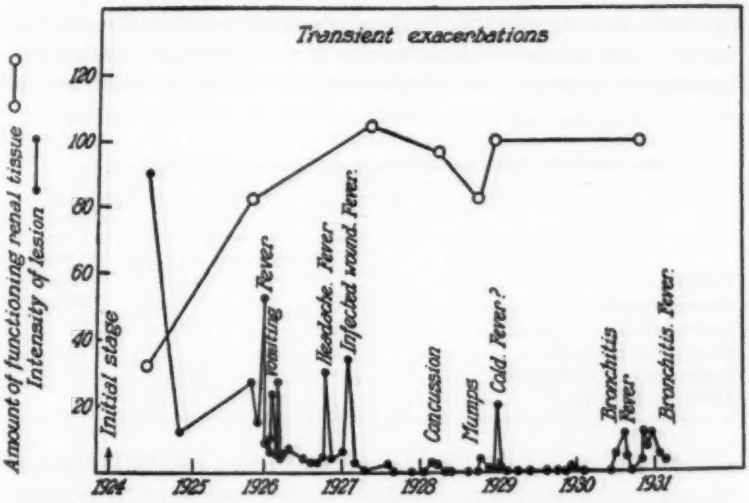

FIG. 11

act for a day or for an hour and the patient for ever after be rid of it, and yet its effect on the kidney might not reach its full fruition until that patient died in uremia twenty or thirty years later. During the initial stage it is possible to picture, in imagination at least, a laying down of hyaline material between capillaries and cells and a thickening of basal membranes, which would constitute a permanent hindrance to the nutrition and renewal of the cells of the kidney, a crippling alteration in environment, entailing a continuous abnormality and slow failure in the maintenance of the complicated and interdependent parts of the renal elements, which in spite of all concomitant repara-

tive mechanisms, might in the end result in an almost complete destruction of the kidney.

It must be admitted that this gloomy hypothesis is not immediately fruitful in the sense of suggesting methods by which it may be tested, except in so far as the fact that it can be even entertained serves to turn attention towards a study of the beginning of the disease. If it is true, one would expect to find that prognosis would vary with the severity of the initial stage. It can indeed be shown that in general the intensity of the initial stage was greater in patients who died later from uremia than in those who recovered, but the result is not at all an impressive confirmation of the hypothesis. There are instances of apparently mild beginnings which ended in death and of

TABLE I

The nature of the illness preceding the onset of haemorrhagic Bright's disease

ILLNESS	PERCENTAGE INCIDENCE
	per cent
Tonsillitis	33
Infected wounds	20
Scarlet fever	16
Fever (cause unknown)	16
Upper respiratory infections	11
Middle ear infections	4

stormy initial stages in which the lesion at last completely healed. General clinical experience certainly suggests that other factors than the initial intensity of the lesion are important in determining the ultimate fate of the patient.

But it may be that our earliest observations are made after the decisive moment has passed. It is almost always only from the history given by the patient that we learn the circumstances which have preceded the symptoms of the initial stage. That evidence is strongly in favor of the view that a streptococcal infection is one of the necessary factors. In 83 per cent of patients who had passed through what seemed to be the initial stage, there was a story of preceding infection. The various illnesses which were reported have been classified in table I although their exact nature was often doubtful. But it is

evident that this series from San Francisco is in general agreement with the observations reported by Dr. Longcope from Baltimore.

But even here where there is substantial agreement about the facts, there remains something hard to understand. Granted that the diseases summarized in table I may all have been streptococcal diseases, and granted that the 17 per cent of patients from whom no history of any preceding illness was obtained may really have suffered from some unnoticed streptococcal invasion, yet even so we reach no unitary origin such as is attained in tuberculosis or in malaria. For we are forced to admit that organisms as diverse as are the haemolytic streptococci of scarlet fever, erysipelas and tonsillitis and the streptococcus viridans may all be associated with the origin of this disease, and that, irrespective of which of these organisms is implicated, the

TABLE II

The interval between the onset of the preceding illness and the onset of haemorrhagic Bright's disease

DAYS FROM ONSET OF THE PRECEDING ILLNESS	PERCENTAGE INCIDENCE
	per cent
0–6	27
7–12	27
8–18	33
19–24	13

disease may be the same in so far as identity can be judged by our present clinical and pathological criteria.

In addition to the doubts engendered by these differences in the bacterial agents associated with the beginning there remains the uncertainty as to the significance of the delay which usually occurs between the onset of the symptoms of the streptococcal infection and the first appearance of the haematuria, hypertension and oedema of the initial stage. This delay has long been recognised for the Haemorrhagic Bright's disease which follows scarlet fever, but there are indications that it also occurs in other diseases. Such rough estimates of the extent of this delay as may be obtained from histories is shown in table II.

The knowledge available is enough to render untenable any simple formulation of etiology. We cannot write "Streptococcal Infection +

Patient = Haemorrhagic Bright's Disease," because it is agreed that, at least in any clinically recognisable form, the disease occurs in only a very small proportion of all cases of scarlet fever or tonsillitis. Even if we introduce "constitutional susceptibility" as a variable, the formula is still too simple. Not long ago I saw identical twins, Irene and Irvine, who together and simultaneously had already passed through several of the diseases of childhood. On the same day the symptoms of a mild scarlet fever appeared in both of them, and they were kept together in bed in the same room. But two weeks later Irene developed the classical symptoms of Haemorrhagic Bright's disease, while Irvine escaped without any signs of a renal lesion. Here the etiological formula would have to be still further complicated, for even when a streptococcal infection is combined with an identical constitution and an apparent uniformity in external environment, there is still no uniformity in the result. We are obliged to suppose that some accidental factor was the determining agent. Many years ago I worked in a recently constructed hospital for infectious diseases. In one of the scarlet fever wards there was a bed called the "nephritis bed" because so many of the children who had successively occupied it had developed nephritis. It was some time before someone observed that this bed differed from the others in being placed in front of a wall ventilator so situated that a draught of cold air from the outside was directed upon the backs of the occupants when they sat up. After the ventilator had been stopped up, no more than the usual proportion of patients in that bed developed nephritis. Whatever degree of truth there may be in this story, for it was never documentarily recorded, it may serve at least as a reminder of the quite unparalleled opportunities for the study of Haemorrhagic Bright's disease which exist in fever hospitals. It is only there that patients can be observed before the disease begins. If their staffs were not so overburdened with routine duties we should not now be ignorant of the general constitutional characteristics and, in particular, of the possible special immunological peculiarities of those patients with scarlet fever who develop the disease.

Thus in its beginning, and even before it begins, throughout its long and curiously changing course, and up to its double end haemorrhagic Bright's disease remains obscure and mysterious. And yet in the

face of all these unresolved doubts and questions this unknown must be "treated." By usage and tradition it is still entirely orthodox to sweat and purge and bleed a patient in the initial stage, to starve him, to force water on him or keep him thirsty. It is probably best to use none of these prescriptions, though it is not certain that some kernel of sense and reason may not lie concealed in one or another of these violent and contradictory procedures. But now the only certainty is our ignorance, and that provides a very good and sufficient excuse for abstention from all forms of treatment which purport to have a direct effect on the course of the disease. Yet it does not condone an absolute agnosticism nor any policy of *laissez-faire*. Even ignorance is limited. In this case it is confined to the special mechanisms of healing and repair. It does not cancel our knowledge of the general principles of nutrition. That knowledge imposes the duty of doing everything possible to meet the minimal food requirements of the patient, and when he is sick and nauseated, that calls for ingenuity and resource. But above all, it necessitates a quantitative dietetics. The risk involved in an interference with the natural instinctive choice of food by the patient on the basis of any therapeutic hypothesis, however plausible, is allowable only if the actual food consumption is measured in order that any deficiency in protein, mineral, vitamine or caloric intake may be recognised and met. This is a binding and stringent requirement because both experimental and clinical evidence tends to show that undernutrition increases the severity of a renal lesion and impedes recovery. Beyond this specific need lie those forms of therapy which are based on the hope that any increase in general well-being may aid the processes of repair. These are useful in the psychological rather than in the physical field and are negative rather than positive. They involve abstention from anything which might waken an unnecesary fear or lead the patient to any anxious consideration of his state. There is nothing we know less about, nothing more admirable than the magnificent adaptation to their slow dying to which so many patients attain. It is surely presumptuous to interfere with the natural growth of that quiet internal comprehension and acceptation by forcing the patient to carry the burden of such unasimilable and mechanistic half-truths as find expression in measurements of the intensity and extent of the renal lesion.

TOTAL NITROGEN AND NON-PROTEIN NITROGEN PARTITION OF GASTRIC JUICE OBTAINED AFTER HISTAMINE STIMULATION[1]

LAY MARTIN, M.D.

From the Chemical and Gastro-intestinal Division of the Department of Medicine, Johns Hopkins University

The total nitrogen figures of gastric juice obtained after histamine stimulation have been reported by Polland, Roberts and Bloomfield (1). Their samples were taken at 10-minute intervals following the injection of the drug. In cases of normal secretion they reported an initial rise in the nitrogen content of the stomach, and a subsequent drop to an amount lower than that found in the fasting specimen. Their limits vary between 40 and 100 mg. per cent. In cases of achylia they found more nitrogen.

An interesting discussion has taken place about the finding of ammonia in the gastric juice. The presence of ammonia in the vomitus of dogs was recognized by Sidney Bliss (2) in 1926 and from these findings the discussion has taken place between its discoverer and Dr. Benedict (3). Certain particulars dealing upon this subject will be discussed in a subsequent paper. Polland, Roberts and Bloomfield (1) in 1928 reported the finding of urea in one case, but did not state the amount or the method. The present report includes the amount of uric acid, urea, ammonia and amino acids and the total non-protein nitrogen in a series of cases from the Gastro-Intestinal Dispensary and the Medical Wards of the Johns Hopkins Hospital.

METHODS

Total nitrogen has been determined for normal gastric juice by the Kjeldahl method.

To obtain a protein-free filtrate it was necessary to devise a method for the precipitation of these materials from a medium with a

[1] Submitted for publication July 10, 1931.

normal hydrogen-ion concentration around 2; in the achylias it was around 7. Blood proteins are precipitated by tungstic acid according to the method of Folin and Wu (4) at a pH of about 7. This method, when applied to gastric juice, in most cases gives no precipitate. Only when the hydrogen-ion concentration has been increased to a pH above 4 is one able to precipitate the maximum amount of protein. Routinely this has been done in the following manner: To gastric juice ½ the amount of 10 per cent sodium tungstate has been added. It is interesting to observe that, as this solution is gradually added, a cloudy precipitate is formed which is reabsorbed as the pH decreases. Two-thirds normal sulphuric acid is then added, drop by drop, until the pH of the solution is brought to about 3.5 From many trials it has been found that this is about the optimal point for the heaviest precipitation. Practically, this end-point can be recognized by means of congo red paper which just begins to turn from light to dark blue. The material is then made to any required dilution, usually about 4 to 1. In the achylias, experience has shown that a 6 to 1 dilution is sufficient. Filtration through a Whatman no. 42 filter paper will usually produce a perfectly clear filtrate. If this does not appear at first, refiltering through the same paper will usually bring about the desired result. Standing overnight in an ice-box will also increase the size of the precipitate particles and make filtration easier.

TOTAL NITROGEN

The figures for total nitrogen in general agree with those of Poland, Roberts and Bloomfield (1), *i.e.*, about 50 to 80 mg. per cent. One fasting juice contained 150 mg. per cent. The amounts found in the achylias, benign or otherwise, were usually considerably higher, reaching about 200 mg. per cent.

FILTRATES

Biuret tests done upon filtrates are negative or show so little color that one feels sure that the amount of protein material can have no significant influence on the findings. A comparison of the biuret reaction on the unfiltered and the filtered portion is sufficient to justify the conclusion that, even when this very faint trace of lavender or pink is seen, the amount of protein therein is certainly negligible.

NON-PROTEIN NITROGEN

The estimation of the total nitrogen on the filtrate was done by the usual Folin and Wu (5) Nesslerization method. In the great majority of cases this substance lies between the limits of 20 and 48 mg. per cent. In uncomplicated or simple achylias, the figures found have

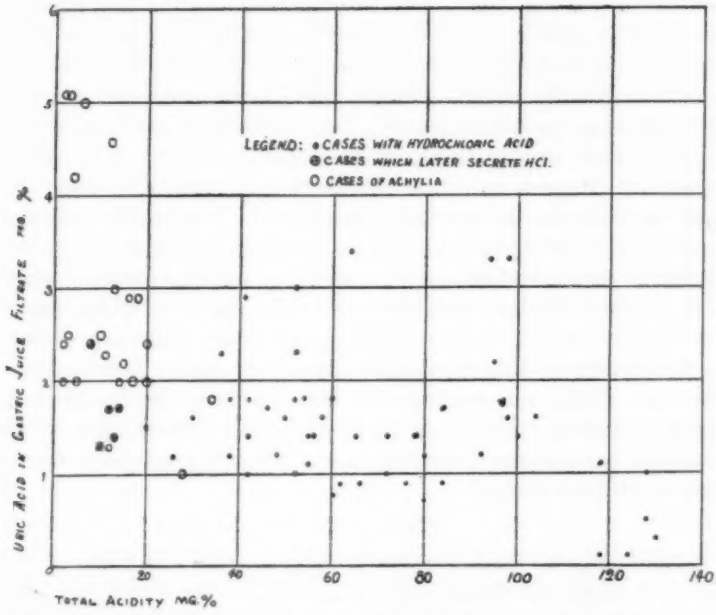

FIG. 1. RELATION OF URIC ACID IN GASTRIC JUICE TO TOTAL ACIDITY

been somewhat higher, between the limits of 30 and 90 mg. per cent. In achylias complicated by or due to carcinoma the figures have been 60 to 150 mg. per cent. In two cases of marked nephritis having a non-protein nitrogen of the serum of 96 in one case, and 160 in the other, the findings in the gastric juice filtrate have been as high as 140 to 180 mg. per cent.

URIC ACID

For uric acid the figures have varied in an interesting manner. In many cases the greater the volume of secretion the less the concentra-

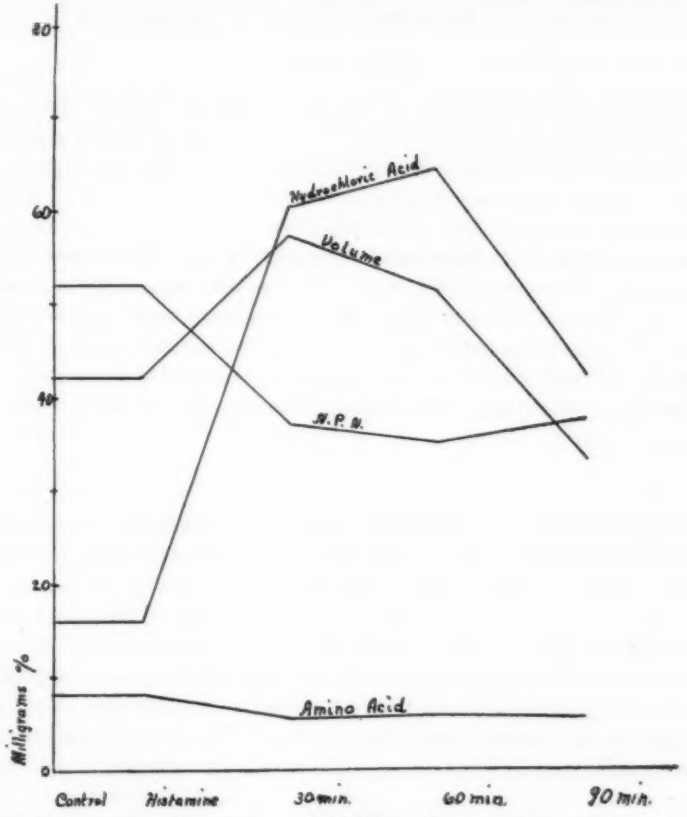

FIG. 2. COMPOSITE CHART FROM 12 NORMAL CASES SHOWING RELATION OF NON-PROTEIN NITROGEN PARTITION TO VOLUME AND ACIDITY

tion of uric acid. In achylias the uric acid has been usually somewhat higher and there has been little variation in successive fractions (fig. 1). Uric acid determinations have been made by the method

of Benedict (6) on both filtered and unfiltered specimens. It is almost invariably true that the amount found in filtered is smaller than that found in unfiltered specimens. There seems to be no doubt that some of the uric acid is carried down with the protein. The average amounts lie between 0.8 and 2.0 mg. per cent.

AMINO ACIDS

The amount of amino acids in the filtrate has been determined by the blood filtrate method of Folin (7). Owing to the higher acidity much more sodium carbonate must be added before the phenolphthalein will impart a permanent pink to the solution. As is true of both non-protein nitrogen and uric acid, there has been a decrease in concentration of these substances with an increase in the volume and titratable acid, as shown in figure 2. In cases of simple achylia there has been less variation although the figures have been higher than those found with a secretion of HCl. The finding of increased amounts of amino acid in cases of carcinoma of the stomach and nephritis is interesting. The normal amounts vary between 2 to 8 mg. per cent.

UREA

Urea is reported as having been found in practically all of the body fluids; consequently it is not surprising that it should be found in the gastric juice. Owing to the relatively large amounts of ammonia the amount of urea was estimated by first determining the amount of free NH_3 plus the amount of NH_3 liberated by the action of urease and from this result subtracting the predetermined amount of NH_3. The permutit method was also tried but was not satisfactory. Urea is usually found in amounts much smaller than those found in the blood, and its place seems to be usurped more or less by ammonia.

AMMONIA

Ammonia has been determined by two methods (1) upon the unfiltered gastric juice by using 5 cc. by the micro-aeration method of Folin and MacCallum (8); (2) upon the filtrate by using the method of Folin and Wu (9). On a large series of cases the results have agreed within narrow limits. It is interesting to observe that there are more

variations in the amount of ammonia than in any of the other non-protein nitrogen constituents. Further findings have suggested reasons for this variation and will be published subsequently. Ammonia has been found in gastric contents in which there was not the slightest trace of bile or trypsin, and it is believed that it is a normal constituent of the gastric juice. It has no connection in these cases with this substance found in the lower intestinal tract. Experiments upon dogs have corroborated this statement and will be published elsewhere. The amounts of this chemical lie between 4 and 12 mg. per cent in normal stomachs.

DISCUSSION

From the findings presented it seems that there is a constant secretion of uric acid, urea, ammonia and amino acids into the normal stomach and that there are rough quantitative limits for each chemical. Of these, uric acid is present in the most regular amounts. The total quantity of the amino acids is variable but generally lies within certain limits. Whether there is HCl present in the specimen extracted is of some importance in interpretation as the amino acids are usually found in increased amounts in the acid-free resting juice of patients who have the ability to secrete HCl after histamine stimulation.

Ammonia is the most variable of the four constituents reported. These figures may be accepted with some assurance for they have been determined by two different methods (1) on whole juice; (2) on the filtrate. The methods are given above.

The determination of urea, on the other hand, is a less satisfactory procedure—if it can be called a procedure at all. It represents the difference between two determinations, ammonia nitrogen plus urea nitrogen (liberated by urease) and ammonia nitrogen. In general the results are accurate but the development of a better method may give more satisfactory results.

It is quite possible that there is some interchange between ammonia and urea within the stomach. This problem is being investigated at present.

The cases are grouped into four divisions.

1. Patients who secrete a so-called normal juice into a stomach which is clinically free from organic disease.

TABLE 1

Data on patients secreting a so-called normal juice into a stomach which is clinically free from organic disease

NUMBER	DIAGNOSIS	TIME	VOLUME	DESCRIPTION	TITER	pH	TOTAL N	FILTRATE	pH	BIURET	URIC ACID	AMINO ACID	UREA	NH_3	UREA + NH_3	NON-PROTEIN NITROGEN	INORGANIC PHOSPHATE
		minutes	*cc.*		*per cent*		*mg. per cent*				*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*
66		F.	10f	Bile +								14.5					
		30	10f	Mucus +++							0.8	7.0					
		60	10f	Mucus +++							1.0	5.3					
67	Neurasthenic	F.	10f	Clear	72–82			Turbid		±	4.2	1.8			9.0	19.9	3.9
		30	10f	Clear	84–94			Clear		±	3.3	1.8			7.2	17.5	3.7
		60	10f	Clear	84–98			Turbid		±	3.3	1.8			6.6	21.2	3.9
								Unfiltered		++++		11.9					
69	Normal	F.	10f	Bile, trace	32–48							2.8			13.8	30.0	6.8
		30	10f	Bile, trace	80–92						1.2	1.1			9.9	16.7	4.1
		60	10f	Bile, trace	68–78						1.4	1.3			7.9	16.7	5.9
73	Chronic appendix	F.	27	Clear, mucus	0–8	6.8		Turbid	4.9	0	2.4	3.7	7.7	1.4	9.1	26.8	6.0
		30	88	Bile, trace, green	86–95	1.5		Clear	3.4	0	2.2	2.2	10.9	Trace	10.9	22.0	6.2
		60	54	Bile, trace, green	108–118	1.4		Clear	3.5	0	1.1	2.8	9.2	Trace	9.2	24.2	3.8
		90	24	Yellow	88–98	1.8		Turbid	3.8	0	1.6	4.1	6.2	5.6	11.8	34.2	4.4
73	After operation	F.	10f	Clear	30–38			Clear		±	1.8	2.6			20.0	49.5	
		30	10f	Bile, trace	50–58			Turbid		±	1.6	3.2			12.5	45.5	
		60	10f	Bile, trace	56–65			Turbid?		±	1.4	2.8			12.5	45.0	

82	Ulcus	F.	10f	Clear	42–55	1.7		Clear	3.5	0	1.1	8.2			17.2	60.0	4.2
		15	10f	Clear	108–118	1.2		Clear	3.7	0	Trace	7.2			12.8	33.0	Trace
		30	10f	Clear	126–134	1.3		Clear	3.5	0	Trace	3.7			10.0	19.0	Trace
		45	10f	Clear	120–130	1.4		Clear	3.4	0	0.3	4.1			12.0	23.5	Trace
		60	10f	Clear	118–128	1.5		Clear	3.6	0	0.5	4.1			12.7	28.2	Trace
85	Normal	F.	10f	Bile, faint trace	14–26	2.4		Turbid	4.5	0	1.2	4.4			9.6	40.0	5.0
		30	10f	Clear	64–76	1.4		Clear	3.5	0	0.9	1.8			6.6	23.0	3.8
		60	10f	Clear	62–72	2.3		Turbid?	4.4	0	1.0	1.3			7.0	21.0	3.8
91	Neurasthenic	F.	50	Clear	52–60			Clear		0	1.8	3.6			5.1	54.0	
		30	35	Clear	46–54			Clear		0	1.8	2.4			3.9	36.0	
		60	35	Clear	78–84			Clear		0	1.7	3.8			3.9	30.6	
		90	20	Clear	32–42			Clear		0	1.8	4.2			7.0	21.0	
96	Ulcus	F.	116	Bile, trace	40–50	1.9		Clear		0	1.6	6.3	0.6	8.4	8.4	30.0	3.0
		30	115	Clear	120–128	1.5		Clear		0	1.0	4.0	3.4	4.2	7.6	20.6	1.9
		60	10	Bile, trace	62–72	1.8				0							2.7
		90	55	Bile	48–56	1.9		Clear		0	1.4	5.8	2.7	9.3	12.0	36.6	2.8
98	Normal	F.	45	Clear	10–20	2.3	75.0	Clear	3.5	0	1.5	6.0	0.4	10.1	10.5	36.0	5.0
		30	50	Clear	70–80	1.6	61.6	Clear	3.6	0	1.2	5.8	3.6	5.6	9.2	33.0	2.4
		60	70	Clear	52–62	1.8	70.0	Turbid	3.4	0	0.9	7.0	0.6	8.4	9.0	35.0	1.5
		90	30	Clear	28–38	1.9	86.6	Clear	3.5	0	1.2	5.9	8.2	5.6	11.8	33.4	3.5
99	Ulcus duodenalis	F.	25	Clear	42–52	2.1	70.0	Turbid		±	1.8	9.0	8.8	5.6	14.4	66.0	1.6
		30	60	Straw	87–97	1.8	76.0	Turbid		0	1.8	6.4	6.4	3.6	10.0	59.8	2.6
		60	60	Straw	94–104	1.8	70.0	Clear		0	1.6	5.0	2.0	10.0	12.0	42.9	1.7
		90	45	Straw	92–100	1.6	77.0	Clear		0	1.4	5.2	5.8	8.0	13.8	36.0	1.5

TABLE 1—*Concluded*

NUMBER	DIAGNOSIS	TIME	VOLUME	DESCRIPTION	TITER	pH	TOTAL N	FILTRATE	pH	BIURET	URIC ACID	AMINO ACID	UREA	NH_3	UREA + NH_3	NON-PROTEIN NITROGEN	INORGANIC PHOSPHATE
		minutes	*cc.*		*per cent*		*mg. per cent*				*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*
104	Normal	F.	19	Yellow, mucus	19–20	2.3	150.0				2.6	8.7		11.2		64.0	4.8
		30	22	Yellow, mucus	76–86	1.5	65.0				1.6	4.9	4.3	5.6	9.9	25.0	2.3
		60	130	Clear	108–116	1.2	60.0				1.2	2.5	2.4	5.6	8.0	25.7	2.0
		90	20	Yellow, mucus	50–60	1.9	84.0				2.3	5.3	7.4	5.6	13.0	50.0	2.9
105	Acne rosacea	F.	25	Mucus	0–0	8.6		Clear									
		30	170	Clear	38–48	2.0	56.0	Clear			6.0	3.8	5.7	5.6	11.3	46.1	4.2
		60	100	Clear	52–63	1.8	52.0	Clear			2.3	2.8	5.3	5.6	10.9	36.6	3.0
		90	80	Clear	60–70	1.6	54.0	Clear			4.6	3.8	10.2	8.6	18.8	39.0	3.1
106	Chronic appendix	F.	80	Clear	0–4	7.8	80.0				2.6	12.2		7.2		70.0	
		30	52	Clear, mucus	14–24	2.4	56.0				3.0	6.5		12.6		36.0	
		60	33	Clear	20–28	2.3	66.5				2.8	9.3		14.0		41.0	
		90	10	Clear	11–20							7.9				43.0	
71	Cholecyst-gastrostomy	F.	6	Mucus +++	6–23	3.4		Turbid	2.5			9.1			21.0	45.0	11.9
		30	3	Mucus +++	8–19	3.4											
		60	18	Mucus +++ bile	63–72	2.0		Turbid	2.5		1.4	5.3			19.7	42.0	7.7
		90	15	Mucus +++ bile	45–55	2.0		Clear	3.4		1.4	8.0			18.7	56.5	7.0
74	Cholecystitis	F., 30		Mucus +++	12–18	3.4		Turbid		0	2.9	6.2			19.2	54.8	9.2
		90		Mucus +++	14–18	3.4		Clear		0	2.4	7.0			17.8	49.4	8.0

76	Cholecyst-itis	F.	19	Clear	58–64	1.7		Clear		0	3.4	5.6				37.5	
		30	21	Bile	6–14	6.9		Turbid		0		10.0			16.4	47.5	
		60	23	Bile +++	0–12	6.8		Turbid		0					13.2		
		90	25	Bile, trace	20–30	2.5		Clear		0		5.8			17.6	52.2	
75	Ureteral-stricture	F.	12	Clear	0–16			Clear		0							
		30	40	Clear	42–52			Clear		0	2.3	9.6			23.4	51.2	
		60	42	Clear	46–52			Clear		0	3.0	12.0			22.0	43.6	
		90	19	Clear	26–36			Clear		0	4.0	6.0			23.5	46.8	
78	Ascariasis	F.	17	Clear	0–13	7.9		Turbid?		0	1.4	11.2			15.8	42.8	7.0
		30	31	Clear	54–66	1.7		Clear		0	0.9	6.8			9.7	25.2	5.0
		60	17	Clear	70–80	1.6		Turbid?		0	0.7	5.6			10.5	36.0	4.6
		90	17	Bile, trace	42–52	1.9		Clear		0	1.0	7.0			11.2	30.0	4.9
79	Neuras-thenia	F.	55	Clear	30–42	2.3		Turbid	3.6	±	1.4	7.0	0.8	11.2	12.0	29.4	4.1
		30	86	Clear	73–84	1.7		Clear	3.5	0	0.9	6.4	4.0	8.0	12.0	23.7	3.3
		60	36	B bile	47–57	2.1		Clear	2.7	0		6.4	8.0	5.0	13.0	28.5	3.0
		90	40	A bile	24–36	2.3		Turbid	3.4	±	2.3	7.0	2.1	11.0	13.1	32.2	4.8
84	Diabetes	F.	38	Bile	0–12	7.9		Turbid		±	1.7	12.9	7.2	16.8	24.0	104.0	5.5
		30	35	Clear	29–41	2.1		Turbid?		±	2.9	8.4	9.2	2.8	12.0	66.0	3.1
		60	26	Clear	32–46	2.0		Turbid?		±	1.7	5.6	13.5	Trace?	13.5	42.6	3.1
		90	40	Clear	0–14	6.3		Clear		±	1.7	4.4	18.7	Trace?	18.5	46.2	4.0

2. Patients who secrete no free hydrochloric acid in the gastric juice but are clinically free from organic disease—so-called benign achylia.

3. Patients having organic gastric disease.

4. Patients having definite disease not of purely gastric origin but which emphatically affects gastric secretions.

The patients in group 1 have been described above. The non-protein nitrogen partition of those falling in the second group is interesting for the reason that there tends to be a higher average for the quantitative amounts of each individual constituent. The amounts are more or less similar to those found in the acid-free resting juice of patients who have the ability subsequently to secrete acid. One case (no. 88) in this group, classed as senility, is a very interesting one, as the various organic substances are present in much larger amounts than in the other members of the group. It may be that some organic pathological condition has been missed. The case is being followed with interest.

To the small series in group 3 are assigned patients suffering from some organic disease including carcinoma, and in one of the cases (no. 90) the differential diagnosis lies between carcinoma and syphilis. The patient was lost sight of before surgery could settle the point. In this series there is a general elevation of the percentage amount of the various chemicals determined. The consistently high content of amino acids is particularly interesting. Uric acid was calculated in only one case and in this instance no increase over the normal was found.

In group 4 interest is centered mainly in the nephritics. These were ward cases with well established diagnoses. In each one of them there was a striking elevation of the whole blood non-protein nitrogen. In these three cases the highest amount of the various substances was demonstrated and it may be that the stomach was acting as an agent for removing these products of metabolism from the body. Whether they are reabsorbed from the lower intestinal tract, whether they are destroyed or benignly conjugated, is an interesting question.

Actually a subtraction of the non-protein nitrogen from the amount of total nitrogen should cover the amount of nitrogen in the protein itself. A study of the figures will show how small a portion of the gastric secretion is formed by this substance. In contrast with the

TABLE 2

Data on patients secreting no hydrochloric acid in the gastric juice but who are clinically free from organic gastric disease, benign achylias

NUMBER	DIAGNOSIS	TIME	VOLUME	DESCRIPTION	TITER	pH	TOTAL N	FILTRATE	pH	BIURET	UREIC ACID	AMINO ACID	UREA	NH_3	UREA + NH_3	NON-PROTEIN NITROGEN	INORGANIC PHOSPHATE
		minutes	*cc.*		*per cent*		*mg. per cent*				*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*
80	Fatigue	F.		Clear, mucus	0–15	7.9		Clear		0	2.2	8.0			8.0	33.0	11.7
		30		Clear, mucus	0–17	6.6		Turbid		0	2.0	6.6			10.0	29.4	8.3
		60		Mucus, green	0–11	7.1		Clear		0	2.3	10.6			13.4	31.8	8.3
		90		Mucus, green	0–10	7.1		Clear		0	2.5	12.0			12.7	41.4	8.3
81	Overwork	F.		Clear, mucus	0–2			Turbid		0	5.1	15.2			13.6	108.0	
		30		Clear, mucus	0–4			Turbid		0	4.2	7.8			18.8	76.0	
		60		Clear, mucus	0–3			Turbid		0	5.1	10.8			13.2	94.8	
		90		Clear, mucus	0–6			Turbid		0	5.0						
88	Senility	F.	16	Light green, desquamation ++	0–10	7.1		Turbid	3.7	0		21.0			48.7	102.0	6.9
		30	12	As above	0–11	7.9		Turbid	3.5	0		19.6			45.0	112.0	6.9
		60	16	As above	0–10	7.9		Turbid	3.5	0		18.0			49.0	123.0	6.4
		90	18	As above	0–8	7.9		Turbid	3.4	0		13.7			60.0	100.0	5.9
107	Benign achylia	F.		Clear	0–8	7.2	77.0				Trace	10.9	7.1	7.0	14.1	56.0	5.7
		60		Bile, trace	12–23	3.7	109.0				Trace	6.5	4.7	7.8	12.5	60.0	2.3
		90		Bile +	0–8	7.2	93.0				Trace	10.9	2.5	14.0	16.5	66.0	4.5
112	Benign achylia	F.	60		0–4	8.4	200.0		3.5		1.3	4.4	2.1	19.6		36.0	9.6
		30	45		0–4	7.8	60.0		3.4		0.9	6.6	0.0	16.8		34.0	6.0
		60	30		0–6	7.8	109.0		3.6		0.9	3.3	3.0	18.6		45.0	8.3
		90	35		0–4	8.4	109.0		3.2		1.0	4.5	2.5	18.7		30.0	6.9

TABLE 3

Data from patients who have organic gastric disease

NUMBER	DIAGNOSIS	TIME	VOLUME	DESCRIPTION	TITER	pH	TOTAL N	FILTRATE	pH	BIURET	URIC ACID	AMINO ACID	UREA	NH_3	UREA + NH_3	NON-PROTEIN NITROGEN	INORGANIC PHOSPHATE
		minutes	*cc.*		*per cent*		*mg. per cent*				*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*
77	Carcinoma of stomach	F.	18	Bile, trace	0–12	7.9		Turbid		0	1.3	16.4			24.0	78.0	
		30	41	Heavy desquamation, bile +	0–28	6.9		Turbid		0	1.0	17.6			16.2	78.0	12.2
		60	27	As above	0–34	7.1		Turbid		0	1.8	16.4			18.0	74.0	11.6
		90	19	Bile, trace	0–10	7.8		Turbid		0	2.0	16.0			21.6	78.0	8.9
90	Carcinoma of stomach or syphilis of stomach	F.		Bile, mucus +	0–11	7.9		Clear		0		23.2			31.5	133.8	6.3
		30		Mucus ++	0–12	7.2		Clear		0		18.0			24.5	63.6	9.8
		60		Clear	0–4	7.2		Clear		0		10.2			23.5	59.9	9.8
		90		Bile, mucus +	0–16	6.9		Clear		0		24.0			24.6	143.2	9.7
109	Carcinoma of stomach	F.	20	Bile	0–1	6.8	154.0	Clear		0		31.0	4.0	17.5	21.5	102.0	2.8
		30	20	Bile	9–20	5.8	218.0	Turbid		±		32.3	27.5	17.5	45.0	149.2	2.7
		60	15	Bile	11–20	5.9	213.0	Turbid		±		30.1	1.0	14.0	15.0	112.5	2.6
		90	30	Bile	0–10	6.8	198.0	Clear		±		27.3	6.6	13.7	20.3	62.5	4.4
111	Carcinoma of stomach	F.	12	Bile	0–6	8.4	180.0					34.8		16.8		74.0	7.6
		60	11	Bile, trace	0–8		145.0					18.0		13.7		60.0	6.0
		90	12	Bile, trace	0–7		106.0					23.4		11.5		62.0	6.4
87	Questionable early carcinoma of stomach	F.	19	Mucus, blood	0–10	7.1		Clear	3.6	±	1.2	17.5			21.0	112.0	4.9
		30	18	Mucus ++++	18–30	2.4		Clear	3.4	±	1.6	16.5			22.0	66.0	4.1
		60	11	Mucus, blood	38–48	2.2		Clear	3.1	±	1.2	23.5			26.0	75.0	2.4
		90	8	Mucus, blood	32–42	2.3		Clear	3.2	±	1.0	23.5			26.5	67.5	

TABLE 4

Data from patients who have marked diseases other than purely gastric, which diseases notoriously affect gastric secretion

NUMBER	DIAGNOSIS	TIME	VOLUME	DESCRIPTION	TITER	pH	TOTAL N	FILTRATE	pH	BIURET	UREIC ACID	AMINO ACID	UREA	NH_3	UREA + NH_3	NON-PROTEIN NITROGEN	INORGANIC PHOSPHATE
		minutes	*cc.*		*per cent*		*mg. per cent*				*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*	*mg. per cent*
70	Pernicious anemia	F.	14	Turbid	0–5	7.9		Clear			2.0	12.0			16.3	49.8	13.8
		30	18	Straw	0–3	7.9		Clear			2.5	7.1			15.0	39.8	12.8
		60	21	Straw	0–2	7.9		Turbid			2.0	6.7			16.0	39.8	
		90	14	Bile +	0–2	7.8		Clear			2.4	7.5			13.8	39.0	13.8
83	Nephritis	F.	17	Mucus +++	0–16	7.2		Turbid		0	2.9	21.0			60.0	107.0	8.3
		30	24	Mucus +++	0–14	7.1		Turbid		0	2.0	18.6			64.0	100.0	8.3
		60	20	Bile, mucus +	0–13	6.9		Clear		0	3.0	14.0			62.0	116.0	4.2
		90	15	Mucus +++	0–12	6.7		Turbid		0	4.6	14.0			68.0	99.0	
86	Nephritis	F.	3	Mucus +++		8.5		Clear		±		17.4				90.0	
		60	7	Bile, trace	0–11	7.0		Turbid		±		33.6			108.0	180.0	5.5
		90	9	Mucus, blood	0–4	7.3		Clear		±		43.6			118.0	180.0	8.3
108	Nephritis	F.	52	Bile ++++	0–8	8.3	148.0			0		30.5	1.8	67.2	69.0	132.0	8.3
		60	22	Bile ++++		8.5	196.0			0		38.8	26.8	102.0	129.0	172.0	4.2
110	Pernicious anemia	F.	15	Clear, mucus	0–13	6.7	82.0	Turbid	3.4	0		17.5		22.4	24.4	64.5	6.0
		90	15	Clear, mucus	0–10	7.5	75.0	Turbid	3.5	0		17.5		20.6	20.6	49.5	5.6

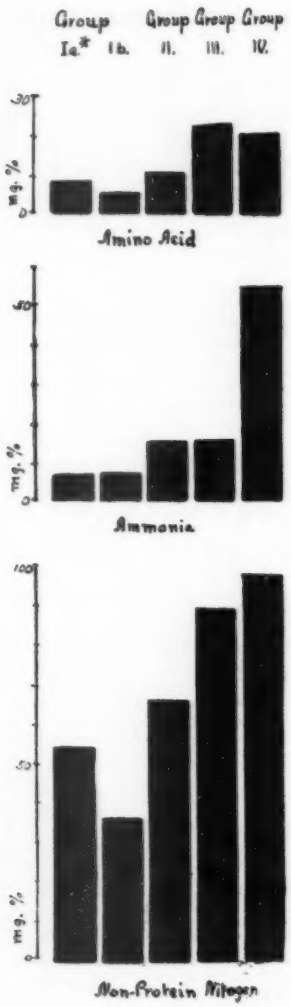

FIG. 3. SHOWING AVERAGE AMOUNT, CALCULATED FROM TOTAL NUMBER PER GROUP, OF AMINO ACID, AMMONIA AND NON-PROTEIN NITROGEN

Group Ia represents the amounts found in the acid-free resting juice of patients who have the ability subsequently to secrete HCl. Ib represents the amounts found in the remainder of Group I. Group II represents amount found in benign achylias. Group III represents amounts found in organic gastric disease. Group IV represents amounts found in extra-gastric diseases as pernicious anemia and nephritis.

method of Bloomfield and Keeffer (5) our estimations have been carried out on material extracted 30, 60, and 90 minutes instead of at 10-minute intervals after the injection of histamine. Consequently we are unable to draw any comparison between our findings and the early findings of these investigators. Within the limits of our method it is possible to see that there is a lowering of the percentage amounts of the total nitrogen, non-protein nitrogen and individual non-protein nitrogen partitions subsequent to the secretion of HCl into the gastric juice. In cases of benign achylia there has been but little variation in the non-protein nitrogen from specimen to specimen. This is also true of various non-protein nitrogen factors. From our findings it would seem that these materials are excreted in the so-called resting juice and that as the volume of the gastric juice is increased by histamine stimulation, the amount of these substances decreases in proportion in content.

If creatinine is present, the amounts are so small that we have been unable to determine it by the method for total creatin and creatinine.

CONCLUSION

1. It is possible to state that during gastric secretion, nitrogen is excreted and that a considerable portion of it is made up of the various non-protein nitrogen constituents, uric acid, urea, amino acid and ammonia.

2. During normal secretion these constituents are present within fairly definite quantitative limits.

3. They are found in higher concentration in benign achylias.

4. In gastric carcinoma and nephritis they are markedly increased.

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BASAL GASTRIC SECRETION IN MAN

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Most of the studies on gastric secretion in man have concerned themselves with data obtained after deliberately stimulating the stomach by means of a test meal or by histamine or some other agent. But even when no stimulus is given and indeed when all controllable stimuli are eliminated, there still exists in most people (see below) a "continuous", "basal" or "fasting" secretion of gastric juice. Such basal secretion may conceivably result from any or all of the following influences: (1) stimulation by autonomic nerves (vagus), (2) stimulation by humoral agents elaborated in the stomach or elsewhere in association with digestion, (3) stimuli due to variations in blood flow in the stomach or (4) "inherent" metabolic activities of the gastric secretory cells. If these influences act in a haphazard or evanescent manner, the amount and character of the basal secretion obviously has little useful significance; if, however, under standard conditions their effect is to produce in any individual a constant and characteristic type of secretion which may be correlated with other biological data from this same individual and with clinical aberrations from normal, then the basal secretion becomes of first importance in the clinical interpretation of gastric disorders. That this may actually be the case will be brought out in connection with the observations herewith reported.

LITERATURE

Beaumont (1) and later Pavlov (2) believed that the stomach at rest produced no true secretion and it remained for Carlson (3) recently to emphasize that even in fasting healthy people there was a slight but continuous production of gastric juice. Carlson found in his subjects with gastrotomy openings that from 10 cc. to 60 cc. of juice was secreted in an hour, and that this was true gastric juice containing

acid and pepsin. Most of the literature on the continuous fasting secretion concerns itself, however, with observations on animals with artificial stomach pouches, and such clinical observations as exist interpret the phenomenon, for the most part, as a pathological one, or at least regard it as due to special stimuli such as those concerned with the so-called psychic secretion. Free secretion of gastric juice in the fasting person, has, for example, been spoken of as gastro-succorrhoea and has been described as a definite disease by Reichmann.

Returning to the animal experiments with artificial stomach pouches, contradictory findings have been reported. It has been claimed, for example, that prolonged fasting diminishes the basal secretion; others have found no change or an increase (4). In man, Hoelzel (5) found, on studying his own fasting secretion, that the acidity was lowered after he had been on a diet containing large amounts of protein and that the acidity was higher after fasting than before. Carlson (4) quotes Luckhardt and Johnstone to the effect that the continuous secretion is increased during hypnotic sleep. Aside from these meager statements we have been unable to find reports of systematic studies of basal secretion in man by means of adequate methods except for the report of Smirnov, Bogdassarov and Tchoukanova (6). These observers aspirated the contents of the stomach over periods of several hours in fasting people and present general data as to the character of the secretion.

METHODS AND MATERIAL

Secretion of gastric juice is known to be modified by various influences aside from the taking of food. Thus, pleasant stimuli associated with the sight, smell or thought of food are said to augment secretion, whereas nauseating and other unpleasant stimuli are said to diminish or inhibit secretion. Mechanical stimulation, as by passing a stomach tube, may increase secretion although associated psychic stimuli may conceivably inhibit. Purposeful studies on the "basal" secretion must obviously, then, be carried out under standard conditions from which such stimuli have as far as possible been eliminated. The following criteria of the basal state were carefully adhered to in the following experiments:

(1) All subjects were quietly in bed in the hospital.

(2) No food or fluid was taken for at least twelve hours before the test.

(3) All psychic stimuli involving apprehension, or suggestion of food, were eliminated as far as possible by quiet surroundings and reassurance. Cases in which the passage of the tube disturbed the subject were discarded.

The technique of the test was as follows: a small mercury-weighted tube was passed into the stomach and the fasting accumulation of gastric juice was withdrawn with a Luer syringe. Continuous aspiration was then carried out and the total secretions were collected over ten-minute periods. The reliability of the results from this point on depends entirely on the skill of the operator, and as we pointed out in a previous paper (7), a great deal of experience is necessary before one develops a tactile sense which enables one to aspirate completely and uniformly. If the procedure is properly carried out, one obtains a regular gradation of secretory volume in successive ten-minute periods. Larger and smaller yields alternating on successive periods usually mean incomplete aspiration. It must be admitted that, at best, a fraction of the secreted juice will escape from the pylorus during this procedure; however, in carrying out a great many tests, often repeatedly on the same subject, it becomes clear that such loss can introduce only a small and uniform error which does not interfere with the comparative value of the data. The subject must be carefully instructed not to swallow saliva during the test and a convenient receptacle for expectoration is provided. Some of the tests are vitiated by regurgitation of duodenal contents, and if bile appears in the aspirated material, the experiment has to be discarded. Regurgitation of duodenal contents *without bile* does not occur in our experience at least as far as can be demonstrated by simultaneous estimations of chloride and free and total HCl. The aspirations were continued over periods of one to two hours or sometimes longer, but no attempt was made to carry on the procedure indefinitely.

The purpose of the present studies was to discover whether the curves of basal secretion, obtained as outlined above, presented any general characteristics or any special characteristics in the individual case. In addition to measurement of volume of secretion, determinations of free and total HCl were made in the usual manner.

RESULTS

When the above procedure is carried out, findings remarkably similar in general character are obtained with most subjects, although there are exceptions which will be described. The usual course of events is as follows:

(1) The fasting accumulation of gastric juice is removed at the beginning of the test. This may vary from a few cubic centimeters up to 100 cc. or more and usually contains considerable mucus and at times some bile. There may be no free acid or the acidity may be quite high, but rarely over 70 to 80 (total).

(2) During the first two or three ten-minute periods of continuous aspiration the volume of secretion usually falls. This variation may be due in part to further residue of fasting contents or to a gradual diminution of the stimulus caused by the passage of the tube. At any rate, as the volume falls, the acidity usually increases and the juice becomes thinner and clearer and contains less mucus.

(3) After a few ten-minute periods a stage of more or less steady continuous secretion is usually reached which represents the "basal" secretion. Volume in successive ten-minute periods is at a practically constant and *minimal* level, whereas acidity is at a fairly constant but *maximal* level. The macroscopic character of the juice varies in different subjects. In some the secretion may contain no visible mucus and looks like spring water; in others it may be opalescent or turbid or may contain considerable quantities of macroscopic mucus. The volume of juice bears no necessary relation to the acidity. This general description can now be supplemented by protocols of individual cases.

DETAILED OBSERVATIONS

Explanation of charts. In the following charts the vertical columns indicate the number of cubic centimeters of juice recovered during successive ten-minute periods of continuous aspiration. The initial shaded columns represent the accumulated fasting secretions which were removed at the beginning of the experiment. Some residues of

fasting contents may still be obtained in the following one or two periods, so that an accurate idea of basal secretion is probably not obtained until the third and later periods.

The solid dots indicate total acid measured in the usual way with phenolthalein as indicator, and the circles indicate free HCl, "dimethyl" being the indicator. The acidity of the fasting contents is to be discounted, since this material contains saliva and at times duodenal contents and, as with volume of secretion, the real acidity of the basal secretion does not become manifest until the third or following period.

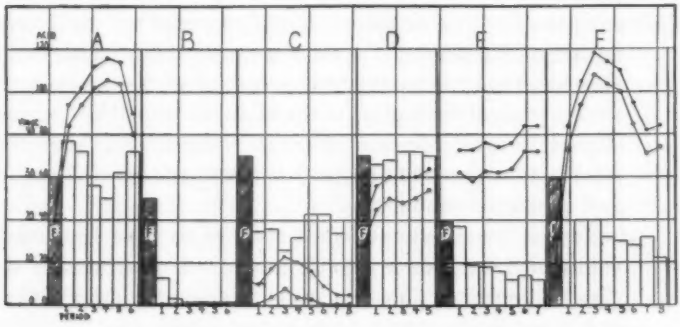

CHART 1. VARIOUS TYPES OF BASAL SECRETION

The following types of basal secretion have been encountered:

1. *High Volume, high acid* (Chart 1, A). The patient was a man of 52 years with a duodenal ulcer. A thin clear juice was obtained in average amounts of about 30 cc. per ten-minute period and the acidity reached nearly 120. Although no test meal or stimulus was used, the figures fall within the upper levels of values obtained after histamine stimulation. This patient's stomach evidently worked constantly at nearly maximum capacity.

2. *Low volume, low acid* (Chart 1, B). A woman of 37 years with mild Graves' disease (B. M. R. +22). There were no digestive symptoms. No free acid was obtained at any time, and after the fasting accumulation was withdrawn, only a few drops of thick mucoid material could be aspirated in each period. Subsequent injection of

histamine showed, however, that this stomach was capable of secreting acid within normal limits. This patient is one of the few we have encountered who had practically no basal secretion.

3. *High volume, low acid* (Chart 1, C and D). No precise relation was found in these studies between the volume of secretion and acidity. The subject illustrated in diagram C was a man of 30 years without digestive symptoms, with a diagnosis of psychoneurosis. Although nearly 20 cc. of juice were secreted per ten-minute period, the highest total acidity was only 23 and the highest free acid was 8. The juice was thin and clear but obviously mucoid. Diagram D refers to a man

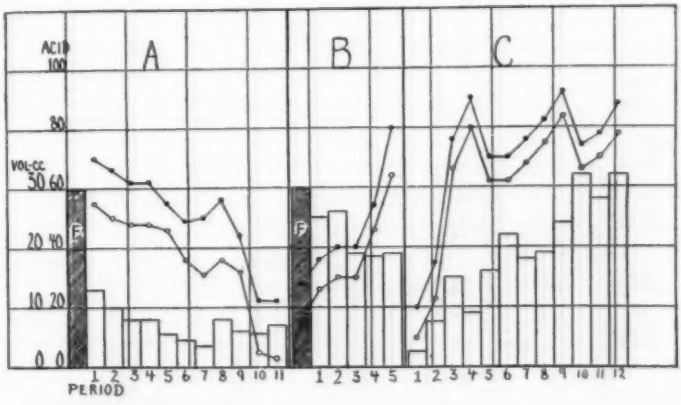

CHART 2. VARIOUS TYPES OF BASAL SECRETION

of 47 years with duodenal ulcer. While the volumes are extremely high—nearly 35 cc. per period—the highest acid value was only 64. The juice was thin and clear.

4. *Low volume, high acid* (Chart 1, E and F). In contrast to the preceding two cases these show relatively low volumes of secretion with very high acid. The first patient was a normal control, a man aged 55 years; the second, a man of 52, with constipation but no stomach symptoms.

The character of individual curves. In occasional cases no steady level of acidity and of rate of secretion is promptly attained. Chart 2A illustrates the findings from a normal man in whose case the acidity

fell steadily, although the volume of secretion remained at approximately a constant level. There was no indication of duodenal regurgitation. In Chart 2, B on the other hand, with high and slightly falling volumes there is a sharp rise in acidity. Chart 2, C, from a man of 37 years with indigestion, shows a steady increase in the amount of secretion, although the acidity remains at a more or less constant high value.

These examples of basal secretion selected from a large number of observations illustrate the wide variety of types which may be en-

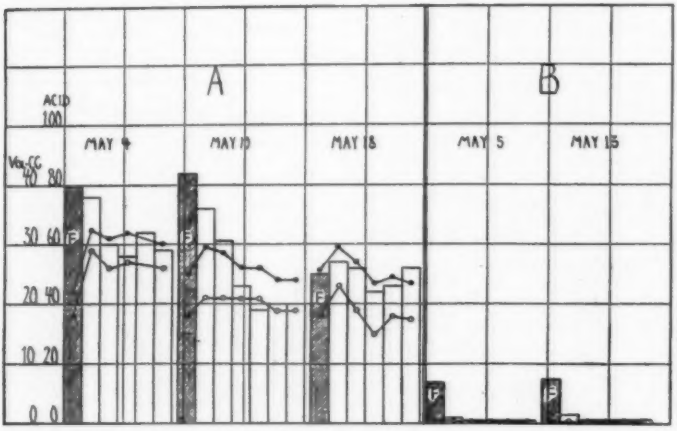

CHART 3. REPEATED BASAL SECRETION FROM THE SAME PATIENT

countered. It is of special interest and importance that most of the subjects, *without any test meal or stimulus*, yield higher acid values than those obtained with the Ewald meal. The futility of the latter procedure, which was fully discussed in a previous paper (8), is again emphasized.

The next question to be investigated was whether the findings in any individual were the expression of haphazard influences, or whether they represented a characteristic response which marked a person from the standpoint of his gastric secretory mechanism and consequently might have practical clinical significance. The point was approached by making repeated tests on the same person at intervals

of several days. It was found that, while there were definite variations, they were restricted to relatively small limits, so that on repeated tests the same secretory "pattern" was always evident. A subject with a free secretion in the first instance, with the rarest exceptions, never showed a low secretion on subsequent occasions or vice versa. This is illustrated by two examples (Chart 3, A and B). The first (A) is of a man of 73 years with a large gastric ulcer. On three successive tests the results were essentially identical. The

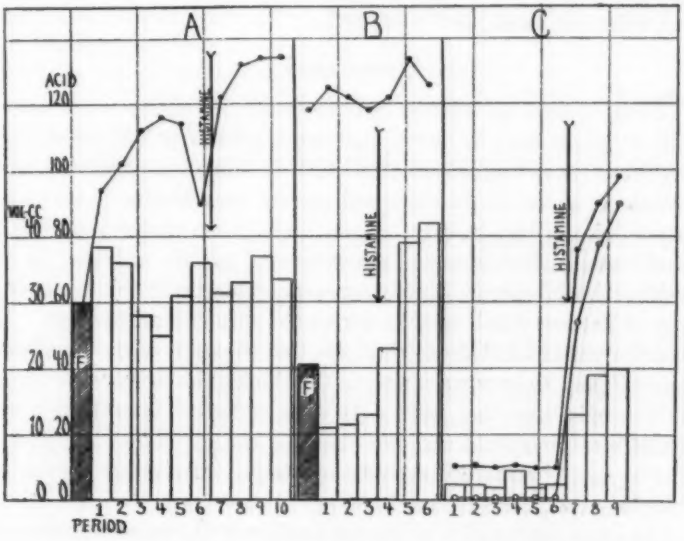

CHART 4. EFFECT OF HISTAMINE STIMULATION ON BASAL SECRETION

second subject (B), already referred to above, gave identical low responses on two occasions, although it was shown by histamine that she could produce a normal gastric secretion.

Relation of basal secretion to histamine response. In some of the cases figured above in which the basal secretion already approached the upper limit of capability of the human stomach one would not expect much additional increase from histamine stimulation. This is in fact the case. Chart 4, A from a man with a duodenal ulcer shows

practically no increase in rate of secretion and only slight increase in acidity over the basal secretion when a large dose of histamine was given. Chart 4, B, from another man with ulcer, shows no marked increase in acidity but a great increase in volume of secretion. Finally, the patient shown in Chart 4, C a young man with chronic arthritis, had minimal amounts of basal secretion with no free HCl, but after histamine he produced large amounts of thin highly acid juice.

Histamine, then, through its powerful stimulating effect tends to wipe out differences in type of gastric secretion which are quite evident when the basal juice is studied.

DISCUSSION

Several points of interest emerge from the above observations. First of all, it may be noted that most normal people under basal conditions (as defined above), and with all stimuli of gastric secretion eliminated as far as possible, still secrete considerable quantities of gastric juice of high acidity, usually higher than that revealed by an Ewald meal. Furthermore, the degree of gastric secretion in any individual, while not absolutely constant, conforms in him to a definite type or pattern which may be correlated with clinical findings. The observations at hand already indicate that the study of the basal secretion will play an important part in the elucidation of gastric disorders and it is of interest that, after sixty years of dispute as to the best form of test meal, it should turn out that one can get quite a satisfactory idea of gastric secretory activity by simply introducing a tube and studying what the stomach is doing.

The exact explanation of the mechanism of the basal secretion and of its variations in different people lies outside the scope of this paper. Indeed the writers do not feel that methods are as yet available to answer the question. It is even uncertain just what part is played by the mere presence of the tube in the stomach. It is evident, however, that the play of autonomic nerves is an important factor, and while one hesitates to become involved in the dubious complexities of "vagotonic" and "sympathicotonic" types, it must be admitted that the free gastric secretion of high acidity which we have found in most cases of peptic ulcer, and which is abolished by atropin, must indicate

a type of vagus activity which is not present in other people who have a low or negligible basal secretion.

In a subsequent paper normal standards of basal secretion and the deviations in disease will be treated statistically.

SUMMARY

1. The secretions of the stomach during the "basal" state have been collected and studied.

2. In most normal people an abundant secretion of considerable degree of acidity takes place, although in some cases secretion is practically absent.

3. Various types of basal secretion are described.

4. Basal secretion in the individual, although variable, conforms to a definite type or pattern.

5. The diagnostic implications of basal secretion are discussed.

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ACUTE EXPERIMENTAL GLOMERULITIS FOLLOWING REPEATED INJECTIONS OF HAEMOLYTIC STREPTOCOCCI INTO THE RENAL ARTERY[1]

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In a previous communication (1), a form of acute glomerulitis was described, which could be produced in rabbits by a single injection of killed suspensions of haemolytic streptococci into the left renal artery. In the normal rabbit this procedure rarely produced a glomerulitis, but in the sensitized rabbit a more or less extensive, and sometimes a diffuse glomerulitis, occurred with considerable frequency. It was suggested that the occurrence of the glomerulitis was probably related to the sensitization of the animal to the haemolytic streptococcus, though it was recognized that the immunological reactions of the sensitized rabbit are complicated, and that it is necessary to take several factors into account in seeking an exact explanation for the origin of the renal lesions. It was observed that the appearance of glomerular lesions was usually associated with the retention of the bacterial bodies in the glomerular loops, and it seemed possible that the condition of the local circulation in the kidney might have some influence on this factor. A series of experiments was therefore devised to determine whether glomerular nephritis could be produced in the normal rabbit by altering the circulation in the kidney. To accomplish this, adrenalin was injected with the suspension of killed streptococci into the left renal artery of rabbits, in which both kidneys were intact, and in some from which the right kidney had been previously removed at operation. In a few experiments the left kidney was subjected to cold during and after the injection. In none of these experiments did the various measures that were employed seem to

[1] Aided by a grant from the Ella Sachs Plotz Foundation.

[2] Jacques Loeb Fellow in Medicine.

influence the retention of bacterial bodies in the glomerular capillaries, and none of the animals showed a glomerulitis.

It was next desired to know what effect would result from repeated injections of killed haemolytic streptococci into the renal artery of the same kidney of a normal rabbit. Experiments of this nature have not, as far as can be found, been previously reported. Though the number of them that could be successfully performed is small, still the results seem sufficiently definite to warrant a description.

METHODS

A strain of haemolytic streptococcus of the B. type, kindly sent by Dr. Shwartzman, was used in this series of animals, and the vaccines were made by the method formerly used (1). In every instance 3.0 cc. of a heated suspension of one 24-hour blood-agar slant, made in 2 cc. of normal salt solution, was the amount injected into the renal artery. The technique of arterial injection has been described. In this series of operations the time of occlusion of the renal artery averaged 30 seconds, and from this there were no notable deviations. Subsequent injections were made into the same kidney (the left) at intervals of seven days. Seven normal rabbits were used and skin tests were purposely avoided before the first injection, but after the first operation a few skin tests were made with broth filtrates. No systematic urinalyses were done, but eleven specimens of urine that were examined at various intervals after the first operation were normal.

The seven experiments may be grouped as follows:

I. The kidneys of two rabbits were examined 7 days after the first injection; both had died on the operating table at the time of the second injection.

II. The kidneys of two rabbits were examined 3 and 4 days, respectively, after the second successful injection.

III. The kidneys of three rabbits were examined four days after the third injection.

An histological examination of the kidneys of these seven rabbits showed the following changes.

The right and left kidneys from the two animals in Group I showed approximately the same appearance. There was some dilatation of a

few tubules in the left kidney, and by bacterial stains many cocci were seen in the glomerular loops. Since the animals died during or immediately after the second injection, the presence of large numbers of bacteria in the glomeruli was to be expected. There were no histological alterations in the structure of the glomeruli, and no changes in the interstitial tissue.

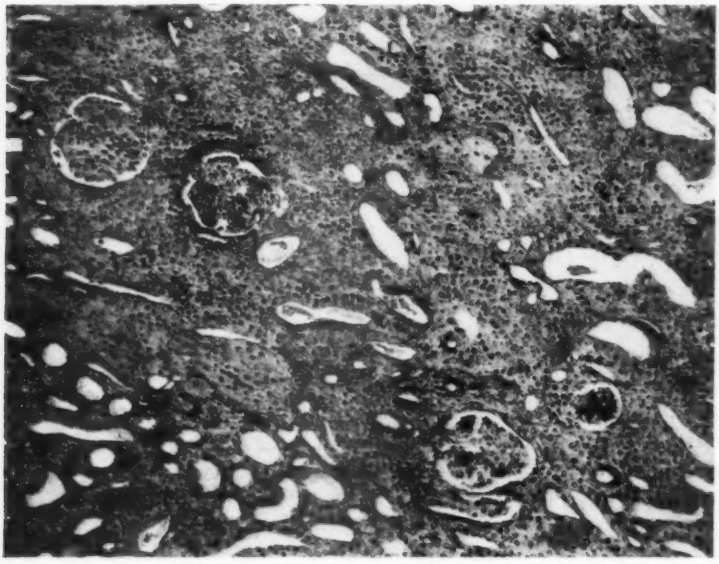

FIG. 1. Rabbit 476. Low-power view of left kidney, 4 days after third injection of dead haemolytic streptococci into left renal artery. Dilatation of tubules, moderate infiltration of small round cells, changes in glomeruli. (Drawing by Mr. Watson.)

The left kidneys from the two rabbits in Group II showed very few changes when compared with the normal right kidneys. In one rabbit the left kidney showed a few collections of small round cells about the blood vessels. There were no alterations in the glomeruli. The left kidney from the other rabbit showed one small infarction but was otherwise normal.

The left kidneys from the three rabbits in Group III all showed more or less extensive changes in the tubules, interstitial tissue and glomeruli. In two rabbits the tubules were frequently dilated and distorted, in the third animal this dilatation of tubules was not so marked. In all three animals there was more or less extensive infiltration of mononuclear cells, collected often in clumps about the blood vessels or glomeruli, but occasionally infiltrating diffusely the interstitial tissue.

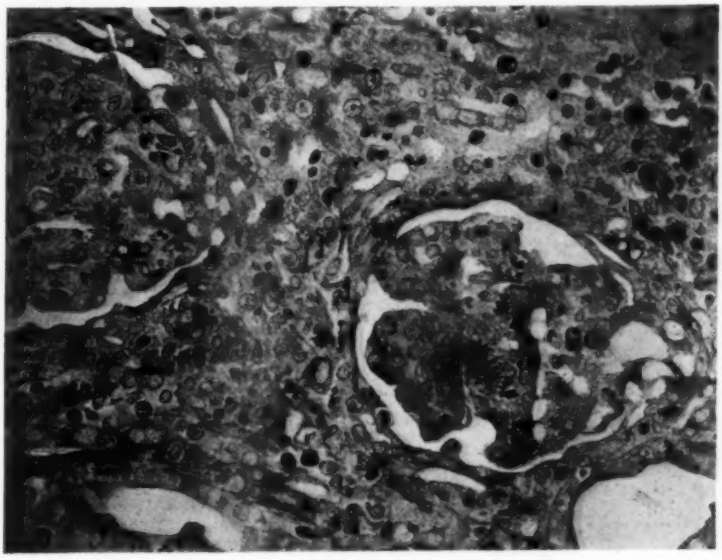

FIG. 2. Rabbit 476. High-power view of two glomeruli shown in figure 1. Swelling of cells, infiltration by polymorphonuclear leucocytes, haemorrhage in one glomerulus. (Drawing by Mr. Watson.)

In all three animals there was more or less extensive involvement of the glomeruli. A large proportion of the renal bodies were involved in the left kidney of one rabbit, while in the left kidneys of the other two rabbits the process was less diffuse. The changes in the glomeruli were similar to those already described, and consisted in the swelling and desquamation of the endothelial cells, the occasional presence of hyaline thrombi, infiltration with mononuclear cells and a few poly-

morphonuclear leucocytes, an occasional haemorrhage in the capsular space and the presence of crescentic formations about the glomeruli. In the left kidney of one animal, one or two blood vessels were thrombosed and the cortical segment supplied by these arteries was in-

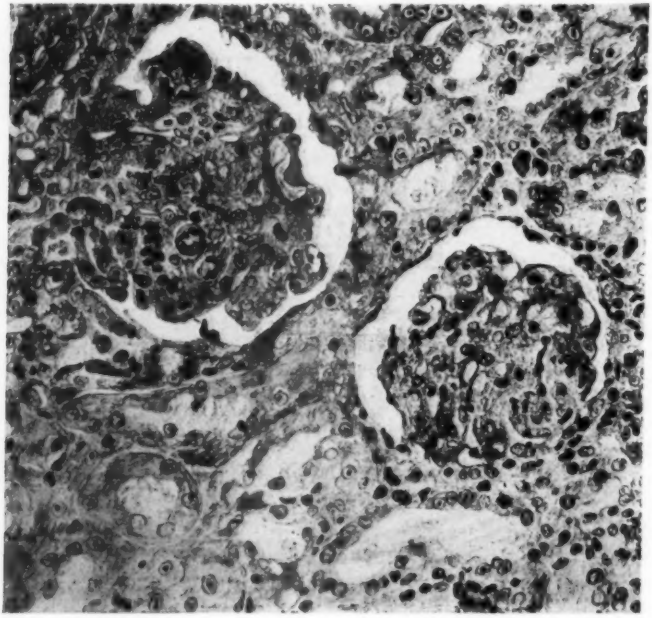

Fig. 3. Rabbit 446. High-power view of left kidney 4 days after the third injection of killed haemolytic streptococci into left renal artery. Two glomeruli showing infiltration by polymorphonuclear leucocytes, thrombosis of capillaries and small areas of necrosis. (Drawing by Mr. Watson.)

farcted. In bacterial stains, organisms could not be found (figs. 1, 2 and 3).

DISCUSSION

These experiments demonstrate that repeated injections at weekly intervals of killed haemolytic streptococci into the renal artery of rabbits result in an inflammatory process affecting both the glomeruli

and the interstitial tissue, and lead, moreover, to changes in the tubules with cast formation. These observations, furthermore, indicate that this inflammatory process does not start with the first injection and progress after subsequent injections; but suggest, instead, that the first two injections cause insignificant or minimal changes, and that the extensive and acute alterations occur suddenly after the third injection. Under the conditions of the experiment, one cannot be sure that this is actually what happens, for to exclude the possibility of a gradually progressive lesion, it would be necessary to examine the same kidney after each injection. The technical difficulties of carrying out such a series of experiments in the rabbit practically excludes the employment of such a method.

Since the histological changes in the kidney are almost exactly the same as those previously obtained in the sensitized or infected rabbits, it seems probable that somewhat similar alterations in the reactivity of the kidney were induced locally by these repeated intravascular injections, as occurred when an infection was set up in the skin of rabbits by the intradermal injection of living haemolytic streptococci. Under these circumstances the inflammatory reaction in the kidney, found after the third injection of killed haemolytic streptococci into the renal artery, might be considered as analogous to the Arthus phenomenon. The changes previously described as occurring occasionally in normal animals, after a single injection of vaccine, are not imcompatible with this idea, since Arthus observed transient inflammatory reactions following the early injections of foreign protein, which, however, increased with repeated injections to a stage of necrosis.

In support of this view there is some evidence to show that with the repeated intraarterial injections, the skin of these rabbits became sensitive to the bouillon filtrates of this strain of haemolytic streptococcus. No skin tests were made before the first injection, but within five days after the first injection the skin of six rabbits was tested by an intracutaneous injection of 0.5 cc. of a filtrate of an 18-hour bouillon growth of the Shwartzman strain of haemolytic streptococcus. One positive reaction was obtained three days after the first injection and one positive reaction five days after the first injection. The tests in the remaining four animals were negative. These four rabbits were again

tested six to ten days after the second injection and at this time they were all found to give positive reactions. It is apparent, therefore, that some change in the reactivity of the skin took place following the intraarterial injections.

It is known that reactions similar to the Arthus phenomenon may be obtained experimentally in the organs of the body. The whole complex subject has recently been reviewed by Nordmann (2). Hepler and Simonds (3) describe areas of necrosis and haemorrhage in the kidneys of rabbits which followed the direct injection of horse serum and egg albumen into the kidneys of animals which had previously received 1 cc. horse serum or 2 cc. albumen at five to six day intervals subcutaneously. Long and Finner (4) produced inflammatory or tuberculin-like reactions in the kidneys of tuberculous pigs by perfusing tuberculin into the renal artery. Seegal and Seegal (5) have been able to sensitize locally the eye of the rabbit to various antigens, such as horse serum, egg-white, casein, the red blood cells of the guinea-pig and of the sheep, and to a strain of haemolytic streptococcus, by the introduction of these substances into the anterior chambers. The subsequent intravenous injection of each of these antigens resulted in an acute sterile inflammatory reaction in the eye. The reactions were specific. These authors discuss the previous work which has been done in attempts to produce local sensitization of the eye. Choi (6) describes an area of haemorrhage and inflammation caused by the injection of horse serum directly into the liver of rabbits sensitized to this protein.

It seems possible, therefore, that one may induce a reaction in the kidney analogous to the Arthus phenomenon by the injection of dead haemolytic streptococci, at weekly intervals, directly into the renal artery.

CONCLUSIONS

A diffuse glomerulitis and interstitial inflammatory reaction could be obtained in the kidney of the rabbit by the repeated injection, at weekly intervals, of killed haemolytic streptococci into the left renal artery. This reaction was not observed after the first or after the second injection, but occurred in all of three rabbits four days after the third injection.

It is suggested that the reaction is analogous to the Arthus phenomenon which occurs under these conditions within an organ.

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THE EFFECT OF TISSUE EXTRACTS ON THE RESPIRATION OF TUMOR TISSUES[1]

L. J. SOFFER, M.D.[2]

From the Chemical Division of the Medical Clinic, Johns Hopkins University and Hospital

Harrop and Barron (1) have shown that the oxygen-consumption of adult non-nucleated red blood cells can be markedly increased by the addition of methylene blue in low concentration. They found that the addition of small quantities of the purified dye in concentrations varying from 0.005 to 0.0005 per cent at 37.5°C. caused an acceleration in respiration that approximated the normal respiration of nucleated red blood cells of birds. The effect of methylene blue is somewhat less striking at room temperature. Hemolyzed red blood cells exhibit very slight if any changes in oxygen-consumption with vital dyes. Methylene blue, however, is capable of enhancing an artificially lessened oxygen-consumption, provided the cell structure remains normal. Thus, respiration, almost totally inhibited by the addition of potassium cyanide in a concentration of 0.005 molar solution, is strikingly increased by the addition of the dye. This effect of methylene blue is equally exhibited by other vital dyes reversibly oxidizable and reducible, such as toluylene blue and to a lesser extent by O-chlorophenol, indophenol, and phenol-indophenol. The intensity of the effect seems to depend on the potential range of the dye. These facts have been abundantly confirmed (2, 8).

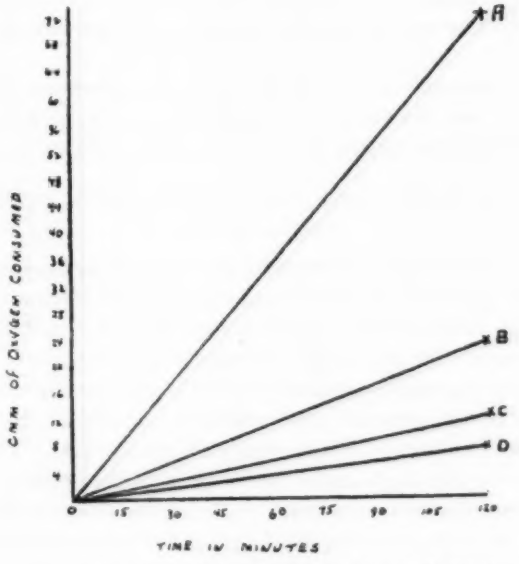
Recently, Michaelis and Salomon (2) have demonstrated that a watery extract could be obtained from various organs that increased the oxygen-consumption of non-nucleated red blood cells exactly as does methylene blue. The liver is particularly rich in this substance, whereas kidney extract exhibits this catalytic effect to a much smaller extent. Spleen, testicle, and lymph node, according to the above authors, are next in order, while brain and muscle show little or no

[1] Submitted for publication July 10, 1931.

[2] Assistant in Medicine, Johns Hopkins University.

effect. Michaelis and Salomon call this active substance "Respiratory Supplement." The effect of the liver supplement on erythrocytes is even more striking than that of methylene blue at 37.5°C., while at room temperature the supplement produces only a slight increase in respiration. The problem as to the character of the activating sub-

FIGURE 1



A - EFFECT OF RAT LIVER EXTRACT ON HUMAN ERYTHROCYTES
B - EFFECT OF RAT KIDNEY EXTRACT ON HUMAN ERYTHROCYTES
C - EFFECT OF HEART MUSCLE EXTRACT ON HUMAN ERYTHROCYTES
D - NORMAL BLOOD CONTROL
37.5°C

stance is of interest. The above authors point out that the respiratory enzyme of Warburg (3) and the respiratory supplement are not identical, since the action of Warburg's enzyme is strongly inhibited by carbon monoxide but is accelerated by light. The supplement acts equally well in the presence or absence of carbon monoxide, and as well in the dark as when exposed to an illuminating bulb. Incidentally,

methylene blue exerts an even more pronounced effect when subjected to a strong light. Again, too, the coenzyme of Harden and Young (4), found so abundantly in muscle, seems to bear no resemblance to the respiratory supplement since the latter is contained very scantily, if at all, in muscle. Michaelis and Salomon in further investigating the character of this substance found that heating the extract to 80°C. destroys the activating agent. Further, when rat liver is ground in a mortar and extracted with acetone, neither the acetone insoluble residue nor the acetone extract exercises any pronounced effect.

We have been able to confirm the marked accelerating effect of rat liver extract, and the lesser effect of kidney extract, on mature mammalian erythrocytes as described by the above authors (fig. 1).

THE EFFECT OF ORGAN EXTRACT AND METHYLENE BLUE ON TUMORS AND NORMAL TISSUES

In view of the effect of methylene blue on the oxygen-consumption and aërobic glycolysis of mammalian erythrocytes, Barron (5) studied its effect on tumors which possess a high aërobic glycolysis, and on normal tissues. He found that the oxygen-consumption of tumors is considerably increased by the addition of the dye, the effect being quite analogous to that exerted upon mature mammalian erythrocytes, though the acceleration is not nearly so pronounced. The normal tissues, on the other hand, show no change with the possible exception of the spleen and the gray matter of the brain which exhibit a slight increase. He concluded that vital dyes, which are reversibly oxidized and reduced, catalyze the oxidative processes of living cells only when those cells possess an aërobic glycolysis. This is further borne out by the fact that normal adult rat kidney, liver and pancreas, whose oxygen-consumption is not enhanced by the addition of methylene blue, have no aërobic glycolysis, while human carcinoma, rat carcinoma and rat sarcoma have some aërobic glycolysis. There is apparently some rough proportionality between the catalytic effect of the dye and the fermentative power of the tissue studied.

Since both methylene blue and the Michaelis organ extract increase the oxygen-consumption of mature mammalian red blood cells, and the former that of tumors, we felt that possibly organ extracts might

TABLE I

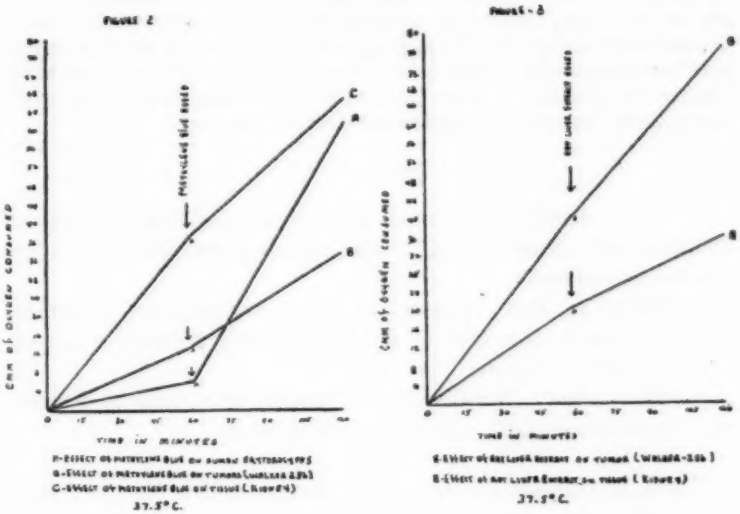
EXPERIMENT NUMBER	EFFECT OF HOMOLOGOUS LIVER EXTRACT ON OXYGEN-CONSUMPTION OF TUMORS AND NORMAL TISSUE			EFFECT OF METHYLENE BLUE—0.005 PER CENT ON OXYGEN-CONSUMPTION OF TUMORS AND NORMAL TISSUES			EFFECT OF HETEROLOGOUS LIVER EXTRACT ON OXYGEN-CONSUMPTION OF TUMORS AND NORMAL TISSUES		
	Oxygen-consumption in c.mm. per hour		Per cent increase or decrease	Oxygen-consumption in c.mm. per hour		Per cent increase or decrease	Oxygen-consumption in c.mm. per hour		Per cent increase or decrease
	Before addition of extract	After addition of extract		Before addition of methylene blue	After addition of methylene blue		Before addition of extract	After addition of extract	
Medullary rat carcinoma—Walker 256									
1	11.7	13.8	+17.7						
2	18.0	17.5	−2.7						
3	20.3	10.5	−48.2						
4	21.0	18.2	−13.3						
5	21.5	15.3	−28.8						
6	12.7	10.3	−18.9						
7	20.8	13.5	−35.0						
8	28.0	35.0	+25.0	9.8	23.5	+139.8			
9	18.5	15.3	−17.3	8.2	10.6	+17.3			
10	22.0	20.5	−6.8	8.5	13.7	+61.1			
11	23.5	30.5	+30.0	10.5	25.0	+142.8			
12	13.0	24.2	+86.1	19.5	28.0	+48.5			
13	17.0	14.0	−17.6	20.5	14.8	−27.8			
14	27.5	13.8	−49.8	12.5	12.7	+1.6			
15	17.0	12.7	−25.2	13.5	10.3	−23.7			
16	10.3	10.8	+4.8	16.0	11.8	−26.2	18.5	16	−13.5
17	12.7	8.8	−44.3				12.5	10.8	−13.6
18	22.0	19.8	−10.0				9.0	10.8	+10.0
Rat sarcoma 338									
1	18.8	11.7	−37.7	5.8	10.7	+84.4			
2	17.0	8.7	−48.8	11.5	12.9	+13.0			
3	24.5	27.4	+11.8	11.3	13.0	+15.0			
4	19.1	17.5	−8.3	29.0	17.0	−41.3			
5	28.0	18.5	−33.8	12.5	11.5	−8.3			
6	30.5	17.0	−44.2	37.0	15.0	−59.4	29.5	22.5	−23.7
7	9.2	9.0	−3.2	18.0	7.5	−58.3	16.7	9.5	−41.3
8	9.0	10.8	+8.8	7.2	8.8	+22.2	15.0	13.0	−13.3
Chicken tumor no. 1									
2				9.4	10.6	+12.7	10.0	7.3	−65.0
				6.0	9.7	+38.3	11.3	4.2	−62.8

TABLE I—*Concluded*

EXPERIMENT NUMBER	EFFECT OF HOMOLOGOUS LIVER EXTRACT ON OXYGEN-CONSUMPTION OF TUMORS AND NORMAL TISSUE			EFFECT OF METHYLENE BLUE—0.005 PER CENT ON OXYGEN-CONSUMPTION OF TUMORS AND NORMAL TISSUES			EFFECT OF HETEROLOGOUS LIVER EXTRACT ON OXYGEN-CONSUMPTION OF TUMORS AND NORMAL TISSUES		
	Oxygen-consumption in c.mm. per hour		Per cent increase or decrease	Oxygen-consumption in c.mm. per hour		Per cent increase or decrease	Oxygen-consumption in c.mm. per hour		Per cent increase or decrease
	Before addition of extract	After addition of extract		Before addition of methylene blue	After addition of methylene blue		Before addition of extract	After addition of extract	
				Adult rat kidney no. 1					
	36.0	30.3	−15.8	39.0	25.3	−35.1			
2	47.0	40.0	−14.8	37.5	32.5	−13.3			
3	38.8	33.7	−13.2	35.0	31.5	−10.0			
				Adult rat spleen					
1	22.0	19.0	−13.6	15.0	7.8	−48.0			
2	28.2	20.3	−28.0	24.5	15.3	−37.5			
3	26.0	15.0	−42.3	22.0	17.7	−19.5			
4				21.0	20.5	−2.4			
5				20.5	17.0	−17.0			
6				22.5	18.0	−20.0			
7				30.0	32.7	+9.0			

exercise a similar effect upon carcinoma and sarcoma tissues. Reference to table I shows that this is not so. Both homologous and heterologous extracts were used. The tumors studied were medullary rat carcinoma (Walker 256) and rat sarcoma (Walker 338). The normal tissues experimented with were adult rat kidney and spleen. With the exception of a few doubtful instances neither the tumors nor the normal tissues showed any change in respiration on the addition of the organ extracts. Apparently the fermentative process which plays a part in the catalytic effect of dyes is not an essential factor where organ extract is concerned. The addition of methylene blue, which was studied simultaneously, showed in the case of medullary rat carcinoma a more or less uniform increase in respiration. This was not entirely true for rat sarcoma 338 where the increase when present was not pronounced and in a number of instances was entirely absent. This is interesting in view of Fleisch's (6) findings that

sarcomata reduce methylene blue rather slowly. Since the speed with which a dye is reduced is a factor in determining its catalytic effect, this may possibly explain its doubtful accelerating action in this instance. Contrary to Barron's findings we could demonstrate no increased respiration when adult rat spleen was treated with methylene blue at 37.5°C., though Murphy and Hawkins (7) have shown this organ to possess a slight aërobic glycolysis.



EXPERIMENTAL METHODS

The experiments were performed on fresh rat tumors and tissues obtained directly after death of the animal by decapitation and immediately studied for their oxygen-consumption in Warburg vessels with Barcroft manometers at 37.5°C. Fresh saline solution containing 0.15 gram per cent of glucose plus 5 per cent of a mixture of phosphate buffers M/15, having a pH of 7.38, was used both for the extract and to dissolve the methylene blue. The organ extracts were prepared essentially as described by Michaelis and Salomon. A small portion of the liver was ground thoroughly in a mortar and ten times its weight of the saline solution was slowly added, the mixture was then filtered and the filtrate used. The sections of tumors studied showed no macroscopic necrosis, and in most instances none microscopically. Bloody tumors were carefully washed until all the blood

had been removed. The capsule of the tumor or tissue was carefully removed. This is important, since the presence of this capsule renders the tissue almost inaccessible to the dye or extract. The tissues were cut into thin slices not more than 0.5 mm. in thickness. The dried weight was 3 to 6 milligrams. These were placed in Warburg vessels to each of which had been added 2 cc. of the saline-buffer-glucose solution. Potassium hydroxide (7 per cent) was used to absorb the carbon dioxide formed. The methylene blue, in concentrations of 0.0025 to 0.005 per cent, and the organ extract were placed in the side arm of the flask. The metabolism of the tumors and tissues was measured in the saline-buffer solution for one hour, after which the extract or methylene blue was quickly added from the side arm and the oxygen consumption further determined for another hour. Freshly prepared methylene blue solution and organ extract was used for each experiment. Both homologous and heterologous liver extracts were employed, the former being obtained from the liver of the rat inoculated with the tumor while for the heterologous extract normal adult non-inoculated rat liver was used.

SUMMARY

1. The accelerating effect of rat liver extract and to a lesser extent of kidney extract on the oxygen-consumption of mature erythrocytes has been confirmed.

2. Methylene blue increases the oxygen-consumption of tumors (of carcinomata more than of sarcomata), while it exercises no such effect on normal tissues.

3. Liver extract, homologous and heterologous, fails to increase the respiration of either tumors or normal tissues.

I wish to acknowledge my sincere thanks to Mrs. Margaret Reed Lewis of the Carnegie Institute for generously supplying me with the necessary tumors and tissues.

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JAMES LAWRENCE CABELL (1813–1889)[1]

WILBURT C. DAVISON

James Lawrence Cabell has never received the recognition which his attainments merit. Born in Virginia on August 26, 1813, he attended school in Richmond, matriculated at the University of Virginia in 1829, obtained his A.M. in 1833 and immediately commenced the study of medicine at the Medical Department there, six years after the admission of the first class. The following year he transferred to the University of Maryland and received his M.D. in 1835. He continued his studies in this country and in France (a student of Louis) and returned to the University of Virginia in 1837 as Professor of Anatomy, Physiology, and Surgery. Nineteen years later he added Materia Medica and Comparative Anatomy to his fields. He retired and died in 1889, at the age of seventy-six, after fifty-two years of active service. Enough for any man to have taught medicine to over half of the classes which have graduated from the Department of Medicine of the University of Virginia, and sufficient that he should have been a pioneer in public health work, but in addition to these adequate reasons for fame, Dr. Cabell's book, "The Testimony of Modern Science to the Unity of Mankind," which appeared in 1859, several months before Charles Darwin published his treatise, "On the Origin of Species by Means of Natural Selection," provides a foundation for modern biological thought, and clearly and brilliantly sets forth his insight into the great changes of evolution. The three following quotations illustrate the breadth and calibre of this great medical teacher:

". . . . these newly acquired characteristics may then be perpetuated by hereditary transmission. . . . . A similar effect is produced in those cases in which a given variation appears accidentally in a single individual and is then transmitted to his offspring" (1).

[1] Address delivered at the dedication exercises of the new buildings of the Department of Medicine of the University of Virginia, Charlottesville, Va., October 22, 1929.

This was publised forty-three years before Hugo De Vries' Mutation theory.

"We may, then, regard it as an established fact that under the influence of causes sometimes appreciable, though often quite unknown, animals may acquire structural characters, differing in many respects from those of the parent stock, and then transmit such peculiarities to their own offspring with entire constancy, so as to give rise to a new breed" (2).

Could evolution be more clearly stated?

"We may remark, in passing, that this tendency to the regular transmission to offspring of characters acquired by the progenitors of a stock, in the gradual process of acclimatization, furnishes an entirely satisfactory explanation of the alleged immunity enjoyed by our negroes from attacks of yellow fever and malarious diseases" (3).

Dr. Cabell's interest in public health and preventive medicine is apparent in this statement of racial immunity made years before Pasteur's publications on bacteriology.

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(2) *Ibid.*, p. 36.
(3) *Ibid.*, p. 39.

BOOK REVIEWS

Tonsil Surgery Based on a Study of the Anatomy. By ROBERT H. FOWLER, M.D. 288 pp. $10.00. (*F. A. Davis Company, Philadelphia, 1930.*)

This is an excellent book and should be read by everyone who attempts to operate on the tonsils. Its chief value lies in the anatomical description, the 102 beautifully executed illustrations, and the statistical data on the health of 1200 children who were re-examined one year after the removal of the tonsils and adenoids. It is from such follow-up studies that the internist, the pediatrician and the laryngologist can form an intelligent opinion concerning the indications and contra-indications for tonsil surgery.

S. J. C.

Principles and Practice of Electrocardiography. By CARL J. WIGGERS. Pp. 226, 61 illustrations. $7.50. (*C. V. Mosby Co., St. Louis, 1929.*)

This book is an excellent attempt to explain the operation of electrocardiographic equipment and the principles involved in the interpretation of the written records. It is usual in such books to find that simplicity has been mistaken for clarity and that the facts have been pruned until they are lean and unintelligible. The author has, however, devoted considerable space to the fundamental facts in physics and physiology upon which the method is based and in ignorance of which the physician is merely "turning knobs and closing switches."

The first six chapters (98 pages) are devoted to electrocardiographic apparatus and technique, to certain factors in physics involved in the taking of records and to excellent descriptions of the equipment. Various commercial types are illustrated and mentioned by name and the differences between them are discussed, but no critique of these differences is provided for the uninitiated. The last 13 chapters (118 pages) are devoted to the interpretation of electrocardiograms and are arranged under the usual headings. The descriptions are clear and the viewpoint conservative. The general excellence of the paper, print and illustrations has doubtless contributed to, what is, in the reviewer's opinion, a rather costly book. The illustrations of electrocardiograms have been reproduced directly from the originals and are not merely scale drawings.

If any criticism can be made, it is in respect to the attitude of the book, which looks upon electrocardiography as a science rather than a method to aid the physician. The practitioner is already bewildered by the host of complex procedures to which he must make his salaams. He knows little of how they can help him and less of their deficiencies. His attitude is often gained from books. On page 144 the following sentences appear. "Objective analysis of a record does not necessa-

rily require any acquaintance with a patient's clinical history; indeed the symptomatology and pathology of the disease may often be read from the record itself." And again, "So the cardiologist is able, from an intelligent analysis of the electrocardiogram, to state the probable pathologic changes existing during life and to outline the probable signs and symptoms which characterize the cardiac affection. Indeed, he can often go farther and predict the probable clinical course which the disease will follow." Such extreme statements reflect an attitude that is not shared by most clinicians who have had extended opportunities to test their experience in the ward and autopsy room, and many will look upon this viewpoint as not only unwise but unnecessary.

D. McE.

Diseases of the Ear. By PHILIP D. KERRISON, M.D. Fourth edition revised and enlarged. 627 pp. $7.50. (*J. B. Lippincott Company, Philadelphia, 1930.*)

This is the fourth edition of Dr. Kerrison's book, which has in the past been regarded as the best American textbook on this subject. It is with great disappointment, therefore, to note that in the present edition there are very few, if any, references to the literature of the subject that have appeared during the past ten years. The only reference to an electric audiometer is on page 87 and refers to a publication in 1919. This is one example of many important omissions that fail to make this edition a modern textbook.

S. J. C.

Otosclerosis. A Résumé of the Literature to July, 1928. Compiled under the Direction of the Committee on Otosclerosis, American Otological Society. Volumes I and II. 684 pp. $15.00. (*Paul B. Hoeber, Inc., New York, 1929.*)

These volumes contain a complete résumé of the literature on otosclerosis up to July 1, 1928. Otosclerosis is one of the common types of deafness that seriously handicaps many thousands of otherwise healthy and normal individuals.

Although this compilation of the literature will be of little practical importance to the practitioner, since no one has ever discovered the etiological agent or an effective treatment for otosclerosis, it is very useful for the purpose for which it was written, *i.e.*, to orient the investigator on the various theories and researches in the past concerning this disease.

S. J. C.

Research and Medical Progress and Other Addresses. By J. SHELTON HORSLEY, M.D. 208 pp. $2.00. (*C. V. Mosby Company, St. Louis, 1929.*)

A collection of addresses by Dr. Horsley ranging from a discussion of the influence of physiologic research on modern surgery to the relationship of politics and medicine.

C. L. G.

Man and Woman. A Study of Secondary and Tertiary Sexual Characters. By HAVELOCK ELLIS. 495 pp. $5.00. (*Houghton Mifflin Company, Boston, 1929.*)

As explained by the author in his preface, this book is a more popular form of the original "Man and Woman" that was published in 1894. It attempts to give the anatomical, physiological and psychological differences between the sexes.

The difficulty of the task is apparent from this quotation from the book. "No two living things are equal, or indeed any single thing always equal to itself; it would be absurd to speak of the "equality" of two whole sexes. We are concerned with masses of values which are unequal and not alike, so that it is constantly being found difficult to apply the same measuring-rod to men and women." This may be illustrated from the chapter on motion. It is apparent to everyone that men are more fitted for muscular exertion than women. Yet when we apply the measuring-rod of output of work per day, women are capable of as much exertion as men. For, as Heymans has shown, women occupy themselves even in moments of leisure, when men seek complete rest, so woman's total activity may be greater than man's. This is especially true in primitive society where men are busy with war and hunting, spasmodic activities interrupted by long periods of rest, while women's work is continuous. Also, as Cathcart found in the tin plate industry, women were able to lift the same total weight per day as the men workers; the men tended to take heavier loads and then rest, while the women worked more steadily.

Although this book is an uncritical summary of the problem of the secondary differences of the sexes, the author attempts to evaluate these differences. It would be especially valuable to teachers in coeducational high schools where they are confronted daily with the problem of the mental and physical development of boys and girls.

C. L. G.

A History of Pathology. By ESMOND R. LONG, Ph.D., M.D. 291 pp. $5.00. (*Williams & Wilkins Company, Baltimore, 1928.*)

In twelve chapters, in a rather small volume, crowded with information, the author presents the names, achievements and writings of some three hundred illustrious men of science. The list includes anatomists, physiologists, chemists, surgeons, clinicians, and pathologists from antiquity to the present time.

Strictly, the book is not a history of pathology, for the history of pathology is the history of medicine, and a description of these men, in chronological sequence, does not quite impart a connected account of the progress of the knowledge of medicine. In something less than three hundred pages, filled with subjects, the characters pass rapidly in review, and the spirit of a literary narrative is lacking. The compact biographical accounts are too brief to make the book a useful reference.

In the concluding paragraphs, discussing the future development of medical science, the influence of organization and capable administration is considered of

importance equal to that of the originality of individual investigators. Many readers may not feel entirely in sympathetic agreement with this idea.

The text is illustrated with many interesting plates. The physical merits of the book are not outstanding, however, and the publishers deserve criticism for producing a rather hasty and insecure binding.

S. B.

Microbiology and Elementary Pathology (for the use of nurses). By CHARLES D. SINCLAIR. 362 pp. (*F. A. Davis and Co., Philadelphia, 1931.*)

As a text and laboratory manual for a brief course in microbiology this book fulfills a definite purpose. It is concise and covers a large field in such a manner as to give a general comprehension of terms, methods and practical applications for one who desires a limited knowledge of the subject. The material consists of brief discussions of bacteriology, immunology, protozoology, as well as a survey of pathology, the last being included as a matter of expediency to cover a course consisting of 45 hours of microbiology and 16 hours of pathology. The text is so condensed that the reading matter is not particularly conducive to further study, but the illustrations are abundant and good, and may serve to arouse the student's curiosity. The important pathogenic organisms are described and the bacteriologic methods used in clinical medicine are outlined. Principles of sterilization and the technique of isolating bacteria in pure culture are the best contributions of the book. The sweeping statements made and the broad generalizations contain a few inaccuracies. The chief criticism of the book is that it treats the field of microbiology as a closed subject.

W. W. F.

A System of Bacteriology in Relation to Medicine. In Nine Volumes. By Various Authors. Prepared Under the Auspices of the Medical Research Council. $31.00. (*His Majesty's Stationery Office, London, 1929, 1930.*)

This review covers volumes 1, 2, 3, 4, 5, and 7, that is, all the volumes thus far issued.

At best the position of reviewer is a delicate one and in the present instance is fraught with special difficulty. That this must be so will be better appreciated when it is understood that the System presents a comprehensive survey of our present knowledge of bacteria with special reference to their relations to the various fields of medical work and that it is the product of the efforts of nearly one hundred British bacteriologists. As a consequence, each article is written by an individual or group of individuals who have taken special interest in that subject and represents the judgment of its authors upon the present state of knowledge in that field based upon the published work of others and their own experience.

At the outset the writer desires to record a keen appreciation of the enormity of the task undertaken by the Medical Research Council and to express his admiration of the brilliant result accomplished. Certainly it is true, as The Earl of Bal-

four says, that there has existed heretofore no comprehensive treatise, in the English language, embodying the results of modern discoveries in bacteriology comparable to these nine volumes. In what follows, therefore, little attempt can be made to do anything but indicate the content of the different volumes and to call attention to what may be considered the feature of each. This must not be interpreted, however, as implying that the articles specifically mentioned are in any way more satisfactory than the others in the volume, but rather that they attracted the reviewer's attention because they were in the field of his own particular interest.

One point in connection with the System that attracts special notice and makes it of unusual interest to American workers is the fact that in the preparation of most of the articles the writers have freely consulted the American literature on the subject. To say the least this is exceptional, as it all too frequently happens that English authors pass over very lightly or completely ignore the American work in the field.

Volume 1 takes up the history of bacteriology—not too much in detail, with special references to the fundamental observations of Leeuwenhoek and the development of the theories of fermentation, spontaneous generation, putrefaction, pyaemia and septicaemia, the evolution of taxonomy, the growth of technique and the epoch-making researches of Pasteur and Koch. Following this are chapters devoted to the morphology and physiology of bacteria with an especially interesting treatment of the Metabolism of bacteria, which leaves one who is not a professional bacteriologist astonished at the multiplicity of activities engaged in by these microscopic forms. Finally, in the chapter on Variation, the much mooted questions of temporary variations, modification, or fluctuation, hereditary variations, causes and modes of variation and the relation of variation to evolution, are discussed. As a whole, this material is treated conservatively.

Volume 2 presents the cocci and hemophilic bacteria. The chapter devoted to the streptococci is written by no less than nine different authors which in itself is indicative of the complexity of the subject. Following this come sections on the pneumococcus, gonococcus and meningococcus. Finally, the hemophilic organisms of the influence group and closely associated types are considered. The treatment of the influence group is particularly interesting.

Volume 3 is devoted to economic bacteriology, plague, anaërobes and food poisoning. The chapter on bacteriology in relation to the application of the science in industry presents an interesting aspect of the subject usually slighted in courses in general bacteriology. The discussion of water and dairy bacteriology certainly presents the subject from an angle that is novel to the American worker in these fields. The chapter on plague is excellent, but if there was nothing else of value in it the treatment of anaërobes as given in the chapters on The Organisms associated with Gas Gangrene, Tetanus and Botulism would amply justify publication of this volume.

Volume 4 covers the enteric group of organisms, the vibrios and the pasteurel-

lae. Typhoid, cholera and dysentery are discussed in detail from every point of view. But of particular interest is the serious attempt at clarification of the relationships of that complex group of organisms included in the group of the Salmonellae with special regard to their antigenic structure.

Volume 5 is devoted to glanders, diphtheria, tuberculosis, leprosy, the Brucellae and anthrax. The discussion of diphtheria is based largely on the monograph, Diphtheria, issued by the Medical Research Council in 1923, with the addition of such material on the subject as has appeared more recently. Nearly 200 pages are devoted to tuberculosis with an added discussion of other diseases in which acid-fast organisms play a more or less important rôle, as in Jöhne's Disease and Leprosy. The material on the Brucella group is good so far as it goes, but the emphasis is almost entirely on the melitensis organisms with comparatively little attention given to the abortus types which may have a much more general significance than has been thought.

Volume 7 takes up the virus diseases and the bacteriophage. The introductory survey of the viruses and virus diseases offers the material of this rather obscure field in a thoroughly readable and apparently authoritative manner. Not only are the virus diseases of man such as smallpox, encephalitis lethargica and acute anterior poliomyelitis included, but also virus diseases of animals, such as rabies and dog distemper, and of plants, as the mosaic disease of tobacco, and of insects as well, as, for example, sacbrood of the honey bee. Finally, there is the bacteriophage. On this subject there has accumulated an enormous literature of recent years and here only the high points of the subject are presented but with sufficient detail to give one a general survey of the field.

In the case of all the subjects presented not the least important feature is the appended bibliography. As a whole the System can be recommended as an admirable addition to the literature of bacteriology and should find a place in the library of every institution where the subject is at all seriously considered.

S. R. D.

Operative Gynecology. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor of Clinical Gynecology, Washington University School of Medicine, and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington University School of Medicine. Fourth Edition, Cloth. Pp. 1078 with 1248 illustrations. $15.00. (*St. Louis; C. V. Mosby Company, 1930.*)

The present edition should prove an excellent reference book for the gynecologist or the general surgeon who does gynecology. Hardly any operative situation which might confront the gynecologist can be imagined for which a solution could not be found in it, and the vast number of operative procedures which are carefully described are just as adequately illustrated. The chapters dealing with the intestinal and urinary tracts as related to gynecology, and those dealing with anaesthesia, are the most noteworthy improvements over the previous editions and leave little to be desired in the way of completeness.

The magnitude of this work removes it from the realm of textbooks and makes it useful only to the already well trained surgeon, for one of little surgical experience in gynecological work would find it difficult to select from the various operations described the one best suited to the case in hand. In view of this fact the more or less elementary chapters on the technique of preparation for operation and the preoperative and postoperative care of patients would seem rather superfluous, inasmuch as one sufficiently trained adequately to appreciate the major portion of the book will have had long practical experience in such details.

H. S. E.

Minor Surgery. By A. E. HERTZLER, M.D., and V. E. CHESKY, M.D. Second edition. Pp. 602, with 475 illustrations. (*C. V. Mosby Co., St. Louis, 1930.*)

As the preface indicates, this volume was prepared primarily to help the dispensary student and the interne, and to be consulted to a less extent by the general practitioner. The first four chapters are devoted to a general consideration of sutures, dressings, bandaging, wounds, blood transfusions, inflammation and infections; the remaining chapters deal systematically with the individual minor surgical conditions found in various parts of the body. Each condition is briefly considered chiefly from the point of view of diagnosis and treatment; the authors have deliberately avoided discussion of the underlying pathology and in this respect have possibly lessened the value of the book to the student. It is obvious that the book is written from a very large personal experience as is apparent not only by the very practical methods of treatment, but also by the numerous good illustrations which are new and which have not been handed down from one textbook to another.

Since the volume was written primarily for the student, it would not have been amiss if the authors had described some of the newer technical procedures which are struggling to get recognition in textbooks. Of these measures may be mentioned the Frisch stitch for tendon suture, but particularly the interrupted end-on mattress stitch which is so extensively used to secure a good scar and which has such a wide sphere of usefulness especially in minor surgery. Although local anesthesia is abundantly advocated in the operative procedures, one feels at times that the promiscuous use of novocain injected directly into acutely inflamed tissues such as those about an ingrowing toe-nail is not always without danger.

As a whole the volume is very complete, readable, a useful addition to the surgical literature and amply fulfills the purpose for which it was written.

F. C. L.